THROMBOEMBOLIC CONDITIONS
AND THEIR
TREATMENT WITH ANTICOAGULANTS

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Preface

EXPERIMENTAL and clinical reports dealing with the phenomena of thrombosis and embolism appeared in the medical literature sporadically following the publication of Rudolf Virchow s classic studies During the past two decades with the greater appreciation of the clinical importance of these phenomena there has been a striking increase in the number of publications pertaining to thromboembolism and to ancillary subjects

The discovery of the anticoagulants heparin and dicumarol provided new tools for investigative work and new agents for the prevention and treatment of thrombosis and embolism in clinical practice The investigation of these agents experimentally and their application clinically resulted in numerous additional reports

It has become difficult for the investigator to keep abreast of developments in the field of intravascular clotting It is impossible for the average practicing physician to study in the original all of the publications devoted to this subject Finally a very considerable number of these papers present conflicting findings and conclusions

It is not surprising that there are differences of opinion among the leading investigators in a field so dynamic and in which so many fundamental principles are as yet not fully understood One barrier to progress is the inadequacy of free and personal communication between workers Despite the amazing development in our modern society of facilities for intellectual intercourse between men the rapidity with which scientific knowledge is now accumulating makes it difficult for the individual to keep pace with current advances Because of differences in elementary viewpoints and backgrounds in training and in specialized interests individual workers tend to pursue their investigations in exceedingly narrow fields and by technical methods so refined by modification that they constitute personal procedures Consequently much current research in this field runs at a tangent rather than supplements existing knowledge and the work of other investi

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state categorically that a prothrombin time of 19 seconds as determined by a one stage method represents a reduction in prothrombin activity to 30 per cent of normal It usually does if determined by Quick s original method utilizing a thromboplastin obtained from rabbit brain But a prothrombin time of 19 seconds determined by the Link Shapiro modification of the one stage method utilizing a thromboplastin obtained from rabbit lung will ordinarily represent a reduction in prothrombin activity to approximately 50 per cent Similarly the belief persists among a few physicians that the relationship between the prothrombin time in seconds and the degree of prothrombin activity in per cent is expressed graphically by a straight line The fact is that this relationship is expressed by a hyperbolic curve and this curve will differ somewhat often considerably when different methods or different thromboplastic reagents are used

The authors have attempted in this monograph to provide a convenient summary of some of the pertinent information collected during the past decades regarding thromboembolic phenomena and the use of the anticoagulants in the prevention and treatment of them and to express briefly the views acquired by a considerable personal experience at the bedside in the laboratory and around the conference table

As far as possible we have endeavored to expose the various facets of matters about which there is debate Where we have felt that our experience has justified an opinion or comment it has been expressed Each chapter is documented to provide the reader with experimental or clinical evidence for the conclusions reached A considerable list of references is appended for the convenience of those who would pursue a particular problem further

This is not a definitive work on the subject of thromboembolism It does not attempt to teach the diagnosis of thromboembolic conditions For such information the reader is referred to the monographs on the peripheral vascular diseases by one of us (I S W) by Allen Barker and Hines and by others It would furthermore be presumptuous for anyone to attempt a definitive work on thromboembolism or anticoagulant therapy at a time

gators Lines of conflict have arisen in some matters which serve more to retard than to stimulate progress

There is no field of medical research or of clinical application in which it appears more difficult to obtain reproducible results *than in the study of blood coagulation and anticoagulant therapy* An essential reason for this is the necessity for meticulous laboratory work Clinical laboratories burdened by the every day demands of the clinician and accustomed by experience to utilize the simplest and most pragmatic laboratory methods available for clinical purposes attempt to determine the prothrombin time in much the same casual manner as they perform a bedside coagulation time or hemoglobin determination In the latter tests as ordinarily performed the range of error is great under any circumstances but the results are sufficiently accurate for practical purposes and there is no particular harm to the patient if errors of ten or even fifteen per cent occur This latitude is not permissible when determining the prothrombin time For example a difference of from two to four seconds in the prothrombin time of whole plasma may represent the difference between normal prothrombin activity and a prothrombin activity which is only one half of normal It has often been difficult for those performing prothrombin determinations for clinical purposes to appreciate the necessity for painstaking technique if accurate results are to be obtained

Uncritical studies which are now appearing too frequently in the literature are the despair of meticulous workers An occasional report indicates the author s complete misunderstanding of current knowledge and of fundamental concepts which are now established facts Erroneous interpretations and beliefs are more common among practicing physicians who are not exposed directly to current advances in the field Two glaring errors are cited as examples of this unsatisfactory state We encounter instances in which the prothrombin time in seconds obtained by a modification of one or another method of performing this determination is compared with similar values in seconds obtained by the original method or a different modification of it Thus a physician will

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WE WISH to express our profound appreciation to these persons and organizations contributing to the development of this monograph to Dr Ralph S Overman for his helpful criticism of certain chapters to Mrs Virginia Butts for typing the manuscript to the American Heart Association the New York Heart Association the United States Public Service and the Lasker and Kress Foundations for support which has helped to make this work possible and to the editors of the Year Book Publishers Inc the *Journal of the American Medical Association* the *American Heart Journal* and the *Stanford Medical Bulletin* for permission to reproduce textual material and photographs published originally by these sources

In addition we are pleased to acknowledge a debt of gratitude to Drs Irvine H Page and A C Corcoran who stimulated the undertaking of this work by inviting us to submit a short monograph for the American Lecture Series As the preparation of the monograph progressed it became obvious that we could not confine the material within a single lecture of this nature This monograph is therefore an outgrowth of their suggestion

C D M

I S W

when these subjects are in so dynamic a state By its continuity this monograph may provide the reader with a more orderly view of the subject than can be obtained by reading the scattered original literature

New York City

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CHAPTER I

Introduction

THE clotting of the blood is an essential physiological process without which man cannot long survive In its absence the slightest injury resulting in hemorrhage permits bleeding to continue until the individual is exsanguinated It is there fore a paradox that more human beings over the age of fifty die as a result of intravascular clot formation than from any other single pathological mechanism

In Ophuls classical analysis of 3000 autopsies (1) in which 1209 (40 1 per cent) of the total deaths occurred in patients fifty years or older nearly one third of all cases examined (30 5 per cent) had manifestly diseased arteries The frequency of generalized arteriosclerosis increased with age from about 25 per cent in patients between the ages of 40 and 50 years to nearly 90 per cent in patients over 70 years

Marked arteriosclerosis of the cerebral arteries was present in 105 instances (3 5 per cent of all cases) and in 50 of these cases (nearly 50 per cent) there were areas of cerebral softening result ing from arterial obstruction Thrombosis of one of the cerebral arteries existed in 8 cases and embolism in 20 cases Thrombosis of the aorta was observed in 5 cases embolic obstruction of the aorta in 2 cases

There were well marked arteriosclerotic changes in the coro nary arteries in 129 instances (4 3 per cent of all cases) approxi mately 10 per cent of all patients over 50 years of age Thrombosis of one or both coronary arteries had occurred in 34 instances and embolism of the trunk or one of the larger branches of a coronary artery was recorded in 6 cases In a group of 70 cases of coronary sclerosis selected for more detailed study the arterio sclerotic lesions in the coronary arteries were severe in 45 in stances and thrombosis had occurred in 20 of these In this selected group 30 patients (42 9 per cent) had died of coronary insuffi ciency 17 of them suddenly and the coronary vessels were severely

diseased in over 90 per cent of these cases An additional 22 (31 4 per cent) of these 70 patients died in heart failure and 18 died as a result of arteriosclerotic changes elsewhere in the body or of intercurrent infection

Embolism of the mesenteric arteries was observed seven times thrombosis twice Multiple thrombosis of the renal arteries was noted in 2 cases while embolism was noted in 15 ten of these being septic emboli complicating endocarditis There were 3 anemic infarcts of the spleen due to arterial obliteration and 34 embolic infarcts for the most part secondary to endocarditis

Arteriosclerosis of the arteries of the extremities was sufficient in 23 cases to produce marked disturbances in circulation Large *arteries of the extremities were obstructed by thrombi in* 13 of the 16 of these cases in which the peripheral vessels were examined adequately There were 4 instances of thrombosis of arteries of the neck or extremities in the absence of arteriosclerosis In brief there were 17 cases of thrombosis of the arteries of the neck or extremities with gangrene of the leg in 11 instances of the foot in 1 of the hand in 2 and atrophy of the arm in 1 Embolism of arteries of the extremities was observed in 7 cases two of these secondary to endocarditis

Simple thrombosis of the heart had occurred in 100 cases (3 3 per cent of all cases) and simple thrombosis of the veins in a similar number of instances although both were found in the same patient on 19 occasions Although local disturbances accounted for 7 instances of intracardiac thrombosis and for 20 instances of venous thrombosis general vascular disturbances accounted for 147 instances (81 per cent) of simple thrombosis of the heart or veins Simple thrombosis in the cavities of the heart was due to cardiac decompensation in 84 cases while thrombosis of the veins was due to cardiac decompensation in 40 cases Venous thrombosis was encountered most frequently in the periprostatic veins of the male (51 cases) in the leg veins (iliac 9 cases femoral 14 cases popliteal 1 case saphenous 1 case unspecified leg veins 2 cases) and in the portal vein (10 cases) where it was most usually due to a local disturbance

Venous thromboses in the lower extremities are found in more than 50 per cent of persons dying of any cause in the latter half

of life (2) These thrombi form first in the smaller veins particularly in the calf muscles in the plantar region of the foot and in the adductor region of the thigh They are found bilaterally as often or more often than unilaterally

Pulmonary embolism is predominately a disease of the latter half of life as demonstrated at the University of Pennsylvania Hospital where 84 per cent of all pulmonary emboli and 92 per cent of all fatal pulmonary emboli occurred in patients above the age of 40 (3)

Although the subject of intravascular clotting has engaged the attention of distinguished pathologists for a century and more—indeed Virchow had explained the pathogenesis of embolism in a series of papers published between 1846 and 1856 thromboembolic phenomena were not recognized clinically with regularity nor was their clinical significance appreciated generally until the past decade

The awakening of professional interest in thromboembolic conditions resulted from the cumulative effect of many independent studies and reports The Scandinavian authors Bauer (4 6) Crafoord (7 12) Frykholm (13 14) Hellsten (15) Zilliacus (16) and their contemporaries emphasized the role of thromboembolism in clinical medicine by painstaking and voluminous reports American authors—Homans (17 21) A W Allen and Linton (22) and Evans (23) in Boston E V Allen Barker and their associates (24 25) at the Mayo Clinic Ochsner and deBakey (26 28) in New Orleans and others published original papers which presaged the veritable flood of articles which have appeared during the past few years

Until recently there had been no means whereby intravascular clotting could be prevented clinically The clinical application of the anticoagulants heparin and dicumarol * is a therapeutic achievement which matches the diagnostic and therapeutic value of recognizing early thromboembolic phenomena Heparin whose anticoagulant activity had been discovered in Howell s laboratory by J McLean (29 30) had been subjected to exhaustive studies particularly in the laboratories of C H Best (31)

Dicumarol is the registered collective trade mark of the Wisconsin Alumni Research Foundation which controls the use thereof

in Toronto Canada and of Erik Jorpes (32) in Stockholm Sweden from whence issued the reports which led directly to the clinical application of this anticoagulant by Murray (33 34) Crafoord (8 12) Wetterdal (35 36) and others The use of heparin was accepted promptly in the Scandinavian countries where the greatest clinical experience during the war years was accumulated

Meanwhile Karl Paul Link (37) and his associates at the University of Wisconsin were investigating in spoiled sweet clover hay the active principle which produces hemorrhagic disease in cattle Link s team of investigators isolated this principle identified it chemically as 3 3′ methylenebis (4 hydroxycoumarin) or dicumarol and synthesized it The initial report by Butt Allen and Bollman (38) that dicumarol is effective clinically was confirmed promptly by Bingham Meyer and Pohle (39) in the fall of 1941 and by E V Allen Barker and Waugh (40) Bollman and Preston (41) and Wright and Prandoni (42) in 1942

Thus the more widespread recognition of thromboembolic phenomena and improved methods of treating these conditions particularly with anticoagulants developed simultaneously The anticoagulants found prompt application in the rapidly expanding knowledge of thromboembolism

The early descriptions of thromboembolic phenomena emphasized particularly the postoperative and the postpartum occurrence of thrombophlebitis with its dramatic sequel pulmonary embolism This emphasis resulted in the widespread application of venous ligation as a prophylactic and therapeutic measure (22 43 48) It is apparent that the problem of thromboembolism is considerably broader than that of thrombophlebitis of the lower extremities It is recognized moreover that thromboembolic phenomena are extremely common and important in patients suffering from medical conditions

Even today the medical profession has not grasped fully the clinical significance of these phenomena Thromboembolism is certainly one of the fundamental pathological processes associated with and indeed producing disease in man It may be the most common pathological cause for serious illness and death For example Tracy Putnam and his associates (19) have summarized evidence to show that vascular destruction or more specifically

TABLE I

ETIOLOGIC CLASSIFICATION OF SUDDEN ARTERIAL OCCLUSION*

- I Embolism
  - A Cardiac
    - 1 Auricular fibrillation, any cause
    - 2 Myocardial infarct with mural thrombosis
    - 3 Mitral and aortic valvulitis
      - a) Bacterial, acute and subacute
    - 4 Failing heart from any cause
  - B Arterial
    - 1 Mural thrombosis
      - a) Aneurysm
      - b) Arteriosclerosis
      - c) Trauma
      - d) Inflammation
  - C Venous
    - 1 Through patent foramen ovale (paradoxical embolism)
- II Thrombosis
  - A Inflammatory
    - 1 Thromboangiitis obliterans
    - 2 Periarteritis nodosa (polyarteritis nodosa, essential polyarteritis)
    - 3 Mycotic arteritis (severe infections)
  - B Degenerative
    - 1 Arteriosclerosis
  - C Traumatic
    - 1 Cervical rib, scalenus anticus, costoclavicular and hyperabduction syndromes
    - 2 External trauma
    - 3 Gunshot and stab wounds
  - D Miscellaneous
    - 1 Infectious diseases
    - 2 Heart disease
    - 3 Blood dyscrasias
    - 4 Surgical procedures
    - 5 Idiopathic thrombophilia
    - 6 Trauma
- III Ligation and severance

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* From Wright, I. S.: *Vascular Diseases in Clinical Practice*, Chicago, Yr. Bk. Pub., 1948

probably a thrombosis of venules is an essential link in the chain of causation of multiple sclerosis and the related encephalomyelitides Thromboembolism is not a disease nor a syndrome it is a fundamental pathological process common to a variety of diseases and clinical syndromes It is the considered opinion of competent observers that we are today only crossing the threshold into a vast field of clinical pathology which evolves from the formation of intravascular clots

TABLE II

ORGANIC (STRUCTURAL) DISEASES OF THE VEINS*

A Obstructive
- 1 Thrombophlebitis and venous thrombosis (phlebothrombosis)
  - a) Primary
    - (1) Thromboangiitis obliterans
    - (2) Recurrent or migrating (without arterial lesions)
    - (3) Essential
  - b) Secondary to
    - (1) Mechanical injury (contusion laceration surgery)
    - (2) Muscular effort or strain
    - (3) Chemical injury (sclerosing agents drugs solutions for diagnosis)
    - (4) Inflammatory or suppurative lesions—infectious diseases
      - (a) Tuberculosis syphilis actinomycosis
      - (b) Other bacteria (to be specified)
    - (5) Severe ischemia
    - (6) Chronic disease of vein wall (varices phlebosclerosis) (Late complications—varicose or postphlebitic ulcers)
    - (7) Blood dyscrasias (polycythemia vera leukemia pernicious anemia)
    - (8) Epidermophytosis (?)
- 2 Neoplastic invasion of vein
- 3 Venous compression—with or without thrombosis or thrombophlebitis due to
  - a) Gravid uterus
  - b) Neoplasm
  - c) Aneurysm
  - d) Scar tissue
  - e) Scalenus syndrome
  - f) Fractures and dislocations
  - g) Increased intra abdominal pressure (ascites etc)
  - h) Extrinsic pressure (tight girdles circular garters poorly made trusses etc.)

TABLE II—*Continued*

B Nonobstructive
  1 Varicose veins (aneurysm)
    a) Primary—congenital incompetent valves
    b) Secondary (to proximal obstructive lesions or pressure)
    c) Secondary to phlebitic destruction of valves
    d) Compensatory dilatation of collateral veins
  2 Arteriovenous fistula
    a) Congenital
    b) Traumatic
    c) Mycotic
    d) Secondary to local disease
  3 Aberrant position
  4 Hypoplasia
  5 Phlebectasia
  6 Periphlebitis without thrombosis
  7 Phlebosclerosis (not usually obstructive)
  8 Rupture

* From Nomenclature Diseases and Abnormalities of the Blood and Lymph Vessels of the Extremities *Am Heart J* 22 519 555 October 1941

Thromboembolic phenomena may be classified in various ways —according to etiology or to anatomical location whether arterial or venous whether peripheral or visceral and whether associated with a medical a surgical or an obstetrical condition Sudden arterial occlusions may be thrombotic in character and may arise as a result of inflammatory or degenerative disease trauma or because of alterations in the coagulability of the blood or in the hemodynamics of the circulation Sudden arterial occlusions may on the other hand be embolic in nature and the emboli may arise from thrombi within the arteries the veins or the chambers of the heart A convenient etiologic classification of sudden arterial occlusion appears as Table I

Venous thrombosis (thrombophlebitis and phlebothrombosis) includes a variety of conditions having different etiologies precipitating factors gross pathology course and prognosis The various etiologic factors and the relation of venous thrombosis to other diseases of the veins are made clear by the classification reproduced in Table II

The relation of sludged blood to the development of throm

boembolic phenomena is not yet clear Although the concept that sludge may form a nidus for the development of an intravascular clot is an intriguing hypothesis it is not proven at the present time that sludging is a necessary precursor for nor even intimately related to intravascular clotting Knisely and his associates (50) have shown that intravascular sludging of blood is demonstrable in a variety of disease processes and their work has been confirmed in general by observations such as those by Loewe and Hirsch (51) in experimental venous thrombosis by Lange and Loewe (52) in experimental frostbite by Knisely et alii (53) in traumatic shock and by Lack and Winsor (54) in hypertension

The exceedingly wide variety of pathological states in which sludging has been observed is perhaps one basis for skepticism *that there is a causal relation between sludge formation and in*travascular clotting Furthermore the erythrocytes which predominate numerically in the sludging process are not known to participate actively in the formation of intravascular clots Indeed they may be relatively absent from the platelet thrombus (white thrombus) One may conclude that while the phenomenon of sludged blood may be exceedingly important and of the greatest significance in relation to intravascular clotting the relationship between the two processes is not at the present time clearly defined

SECTION I

THROMBOEMBOLIC PHENOMENA IN CLINICAL MEDICINE

CHAPTER 2

Venous Thrombosis and Pulmonary Embolism

SINCE the initial intense interest in the problem of thromboembolism centered about the occurrence of venous thrombosis and pulmonary embolism in surgical and obstetrical patients particularly postoperatively and postpartum it is understandable that a tremendous body of medical literature has accumulated on this aspect of the problem It is here that the greatest amount of data has been assembled and the most precise knowledge obtained Space does not permit not would it be worthwhile to review this literature in detail A review of selected studies will suffice to orient the reader

Barker Nygaard Walters and Priestley (25) in the first of a series of statistical studies of postoperative venous thrombosis and pulmonary embolism published in 1940 and 1941 reported statistics obtained from the records of all instances of these complications noted postoperatively at the Mayo Clinic during a thirteen year period Cases studied included those in which there was a clinical diagnosis of thrombophlebitis or pulmonary embolism cases of fatal pulmonary embolism (clinical diagnosis confirmed or established by necropsy in 84 per cent of cases) and cases in which a non fatal pulmonary embolus or an antemortem venous thrombosis or thrombophlebitis was discovered only at autopsy In a total number of 172 888 patients having operations 1 665 patients or 0 96 per cent suffered thrombosis with or without embolism or embolism with or without evidence of thrombosis

The statistics were subdivided so that the number of cases of postoperative venous thrombosis and of pulmonary embolism following various types of surgery could be tabulated Venous thrombosis and pulmonary embolism were found to be relatively twice as common following laparotomy as they were following

all operations and they were three times as common following laparotomy in which operations were performed on the female pelvic organs The highest incidence of venous thrombosis and pulmonary embolism occurred in those laparotomies in which *there was extensive* resection of tissues operations of relatively long duration or operations of relatively great magnitude Venous

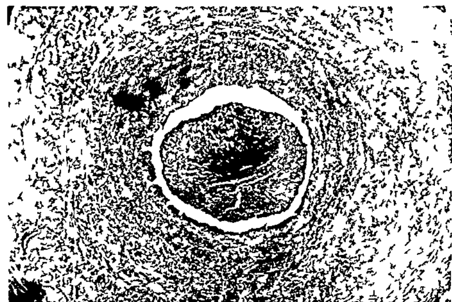


FIGURE 1A Cross section of the tail of a thrombus lying free in a vein Although the thrombus is free at this point the vein wall shows signs of inflammation

thrombosis and pulmonary embolism occurred twice as often in cases of repair of bilateral femoral or inguinal hernia as in cases of unilateral femoral or inguinal hernia

Simple exploratory laparotomies for inoperable malignant le*sions were accompanied by a high incidence of venous thrombosis* and especially of pulmonary embolism The incidence of these complications following resections of the stomach or of the intestines frequently performed for carcinoma was high which suggested that carcinoma might predispose to postoperative thromboembolism The incidence of venous thrombosis and pulmonary

embolism following appendectomy for ruptured appendix was more than twice as great as that following appendectomy for simple chronic or subacute appendicitis supporting the suggestion that the incidence of these complications is greater when infection exists

The authors concluded that postoperative venous thrombosis and pulmonary embolism are more common following laparoto

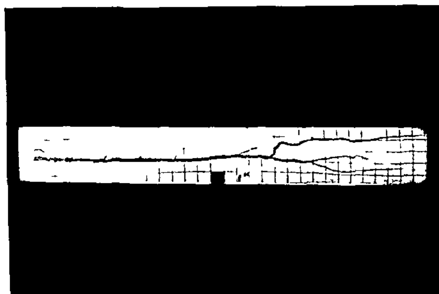


FIGURE 1B An example of propagation of a thrombus to the length of 36 inches This was removed whole from the veins of a leg by suction (Courtesy of Dr Gerald H Pratt) (From Wright I S *Vascular Diseases in Clinical Practice* Chicago Yr Bk. Pub 1948)

mies in which operations are done on the pelvic viscera in which there may be injury or ligation of the iliac veins in operations of great magnitude or of long duration in which considerable tissue is removed or in which there is apt to be a great amount of tissue injury and in patients suffering from carcinoma or infection The actual incidence of these thromboembolic complications postoperatively is small only about 1 per cent in the total series and only about 5 per cent in those operations follow

ing which they were most common The highest incidence of fatal pulmonary embolism following any type of operation is only 0 77 per cent following splenectomy

Hellsten (15) and later Jorpes (32) and Zilliacus (16) using for the most part identical data have summarized statistics from the literature on the incidence of thromboembolic phenomena and on the morbidity and mortality resulting from thromboembolism particularly from pulmonary embolism In general these data are considered in the three separate categories of postoperative postpartum and medical cases A further distinction is made between those statistics collected before or after the introduction of the principle of free mobilization and early ambulation It is to be noted that statistics in any category vary widely from country to country and from clinic to clinic

Jorpes (32) states that during the era of conservative postoperative management (prolonged bedrest and immobilization) about 1 per cent of all surgical cases were complicated by a deep venous thrombosis or a pulmonary embolus and that this incidence was reduced to approximately 0 6 per cent with the introduction of active postoperative care (early mobilization) There is great variation in the incidence of thromboembolism according to the site of surgical intervention since a considerably greater number of thromboembolic complications occur in abdominal surgery than in extraabdominal operations and the highest incidence often from 3 to 5 per cent is encountered following pelvic surgery In selected groups of patients undergoing extensive abdominal operations for carcinoma abdominal hysterectomies prostatectomies and biliary tract surgery the incidence of thromboembolism may reach as high as 9 per cent (11 55)

Zilliacus (16) points out that the frequency of pulmonary embolism in cases of postoperative thrombosis is 50 to 60 per cent and that the mortality of postoperative thromboembolism due largely to pulmonary embolism is in the neighborhood of 20 per cent A high incidence of pulmonary embolism is encountered in obese patients irrespective of the primary surgical conditions (56 57)

The incidence of postpartum thromboembolism also quite variable in different series has probably been reduced to about

0 5 per cent in otherwise uncomplicated deliveries by the policy of early activity and early ambulation The incidence is of course considerably higher in those cases in whom instrumentation or operative intervention is necessary However the incidence of pulmonary embolism is much lower in obstetrical cases than in postoperative cases occurring in from 15 to 35 per cent of cases



FIGURE 2 Thrombus of the left common iliac vein large enough to produce a fatal embolus (Courtesy of Dr John G Kidd) (From Wright I S *Vascular Diseases in Clinical Practice* Chicago Yr Bk Pub 1948)

developing postpartum thrombosis as against from 50 to 60 per cent in postoperative thrombosis and the mortality rate in postpartum thrombosis is also relatively low 3 to 5 per cent as compared to a mortality rate of 20 per cent in postoperative thrombosis according to the Scandinavian authors This relatively low incidence of thromboembolic complications in obstetrical patients may be explained by the relative youthfulness and the generally good physical condition of the parturient patient The size of the originating veins in the pelvis may also be an important factor

Data on the incidence of thromboembolism in medical cases

are not so readily available as are data for postoperative and post partum cases However the relatively high incidence of thromboembolic complications in medical cases has become generally appreciated There is no doubt that thromboembolism and pul



FIGURE 3A Autopsy specimens from a patient with a fatal thromboembolic syndrome Folded embolus 45 cm long that blocked both pulmonary arteries (Courtesy of Dr John C Ladd) (From Wright I S *Vascular Diseases in Clinical Practice* Chicago Yr Bk Pub 1948)

monary embolism are as common among the general population of the medical wards as on the surgical wards

Thromboembolism is seen in all types of patients bedridden for whatever cause but particularly in those suffering from cardio vascular disorders anemia polycythemia dehydration pneu monitis and septic conditions Undoubtedly the incidence of thromboembolism and the mortality resulting therefrom is con siderably higher in selected groups of medical patients namely the aged those suffering from heart disease cancer etc than in almost any selected group among surgical and obstetrical patients Thus of 370 cases of thromboembolism studied by

Hampton and Castleman (58) only 40 per cent occurred in postoperative patients while 30 per cent occurred in patients suffering from heart disease and 30 per cent in patients suffering from general medical conditions Hunter et al (59) stated succinctly



FIGURE 3B Autopsy specimens from a patient with a fatal thromboembolic syndrome Another large embolus coiled in the right ventricle (Courtesy of Dr John G Kidd) (From Wright I S *Vascular Diseases in Clinical Practice* Chicago Yr Bk Pub 1948)

that the greatest single factor favoring thrombus formation in the lower extremity is sudden confinement to bed of a previously ambulatory older person

Bauer (60) found that in a total of 801 cases of thrombosis in the general medical and surgical sections of ten large Swedish hospitals in 1939 448 cases (56 per cent) of the total number occurred in medical cases and of these 79 (18 per cent) died Whereas Axhausen (61) and Hunter et al (2) found little difference betw in i sm in medical

are not so readily available as are data for postoperative and post partum cases. However, the relatively high incidence of thromboembolic complications in medical cases has become generally appreciated. There is no doubt that thromboembolism and pul



FIGURE 3A. Autopsy specimens from a patient with a fatal thromboembolic syndrome. Folded embolus 45 cm. long that blocked both pulmonary arteries. (Courtesy of Dr. John C. Kidd.) (From Wright, I. S.: *Vascular Diseases in Clinical Practice*, Chicago, Yr. Bk. Pub., 1918.)

monary embolism are as common among the general population of the medical wards as on the surgical wards.

Thromboembolism is seen in all types of patients bedridden for whatever cause, but particularly in those suffering from cardiovascular disorders, anemia, polycythemia, dehydration, pneumonia, and septic conditions. Undoubtedly the incidence of thromboembolism and the mortality resulting therefrom is considerably higher in selected groups of medical patients, namely the aged, those suffering from heart disease, cancer, etc., than in almost any selected group among surgical and obstetrical patients. Thus, of 370 cases of thromboembolism studied by

original level at which such thrombi are formed the majority of pulmonary emboli originate from thrombi which have developed in or propagated to the femoral veins This is evident when massive pulmonary emboli are examined postmortem the average thickness is found to correspond to the width of the femoral vein Fatal pulmonary emboli almost always occlude the main trunk of the pulmonary artery or two or three of its main branches involving a plug of tremendous bulk These plugs are composed primarily of folded fragments of thrombus a finger s breadth in diameter but of very great length frequently 35 to 45 cm

Stasis is the most common factor leading to the development of the spontaneous thrombi which originate in the femoral veins and produce pulmonary embolism irrespective of the primary disease or of the operative procedure In a large per cent of fatal pulmonary emboli following femoral vein thrombosis the patient has been forced by circumstances shortly before death to maintain an unusually cramped position Systematic manipulation of the lower extremities will therefore reduce the hazard of thrombus formation and of subsequent embolization

These statements do not apply with the same emphasis to the inflammatory type of acute thrombophlebitis or to septic thrombi The former are more apt to be more firmly attached to the wall of the vein and therefore are less apt to produce emboli The latter are serious because of the hazard of pyemia Nevertheless it is impossible to predict which thrombosis may give rise to a fatal pulmonary embolus Therefore all must be treated with the same serious respect

and in surgical cases Belt (62) and Breslich (63) found that pulmonary embolism is even more common in patients dying of medical conditions than in those dying after operations

There are two points which require emphasis to shake the complacency of those who are impressed by the relatively low over all figures provided by many large statistical series The first is that once intravascular clotting has occurred the frequency of subsequent pulmonary embolism is alarmingly high and the

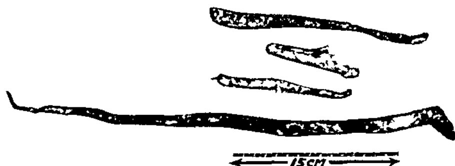


FIGURE 3C Autopsy specimens from a patient with a fatal thromboembolic syndrome Emboli shown in Figure 3A and Figure 3B and others from the same patient (Courtesy of Dr John G Kidd) (From Wright I S *Vascular Diseases in Clinical Practice* Chicago Yr Bk Pub 1948)

mortality rate from these pulmonary emboli runs from 5 to 20 per cent Secondly when a careful search is made at autopsy for evidence of antemortem thrombi the number of intravascular thromboses found is astonishing Thus Rossle (64) found that the calf veins contained thrombi in 27 1 per cent of 324 patients over 20 years in age and Hunter et al (2) found thrombosis of the deep veins of the leg in 52 7 per cent of 351 middle aged and older patients forced to bed for varying periods of time Undoubtedly intravascular clotting occurs far more commonly than is recognized clinically or is discovered by routine postmortem examination In many cases the condition subsides spontaneously and without complications

The hazard of fatal pulmonary embolism is particularly great following the development of spontaneous venous thrombosis in the leg veins the so-called phlebothrombosis Irrespective of the

quency in association with arteriosclerosis obliterans is augmented by the frequency of debilitation in the aged and by the high incidence of diseases of the veins such as varicose veins in the older patients

Whereas arterial occlusion by thrombus formation is by far most commonly the result of peripheral vascular disease or local vascular disorder peripheral arterial occlusion due to embolism is almost always the result of heart disease Indeed in the Mayo series 41 of 46 sudden arterial occlusions due to embolism were produced by emboli originating in the heart Peripheral emboli occur as complications of a variety of cardiac conditions notably in the presence of the cardiac arrhythmias particularly auricular fibrillation in endocarditis and valvulitis whether on an infectious or on a rheumatic basis in coronary occlusion with myocardial infarction and in congestive heart failure when the slowing of the blood stream predisposes to the formation of intravascular clots

In a series of 98 patients suffering arterial embolism Warren and Linton (66) found that in 87 patients (88 7 per cent) a clinical diagnosis could be made which gave presumptive evidence of an intracardiac source of the embolus In 64 cases there was auricular fibrillation in 15 cases myocardial infarction and in 1 case both auricular fibrillation and myocardial infarction In 7 cases subacute bacterial endocarditis was presumably the cause of the embolism in 11 cases the cause was undetermined but in only 2 of these did all cardiac causes seem to be excluded The greatest incidence of arterial embolism in this series was in the fifth and sixth decades

Systemic embolization is an important complication of auricular fibrillation the source of the embolus ordinarily being a mural thrombus in the left auricle or left auricular appendage Similarly pulmonary embolism occurs as the consequence of a right auricular thrombus Less commonly the mural thrombi develop in the ventricles Auricular thrombi are found in approximately 43 per cent of patients with rheumatic heart disease and auricular fibrillation (67)

As mentioned previously in the series of Warren and Linton (66) auricular fibrillation was present and was presumably the

CHAPTER 3

Thromboembolic Phenomena in Cardiovascular Diseases

THROMBOEMBOLIC phenomena are frequent and serious complications in a variety of peripheral vascular diseases particularly in those of an obliterative nature but occasionally in the vasospastic diseases as well Arterial occlusions phlebothrombosis and thrombophlebitis are extremely common incidents in the natural history of the obliterative vascular diseases commonly seen in the lower extremities

Arterial thrombosis is an almost invariable accompaniment of *advanced* arteriosclerosis obliterans and *sudden* arterial occlusions are encountered in at least 10 to 20 per cent of all cases of either arteriosclerosis obliterans or thromboangiitis obliterans (Buerger s disease) In one hundred cases of sudden arterial occlusion studied at the Mayo Clinic (65) occlusion occurred in the presence of a well defined arteriosclerosis obliterans in 33 instances In all of these cases but one which was the result of an embolus the occlusion was thrombotic in origin Many arterial occlusions occur slowly as the result of the growth of mural thrombi superimposed upon atheromatous plaques The signs and symptoms of occlusion appear with the final closure of the vessel

Less commonly sudden arterial occlusions occur secondarily to the various forms of arteritis notably periarteritis nodosum and mycotic arteritis to aneurysm or to the neurovascular syndromes of the shoulder girdle As a rule the vascular occlusions encountered early in the vasospastic diseases are confined to the smaller vessels and play a role in the development of local lesions and do not produce systemic manifestations until the disease is advanced

Thrombophlebitis occurs at one time or another in at least 40 per cent of all cases of thromboangiitis obliterans Its fre

are essentially symptomless and unrecognized until embolism occurs

Thromboembolic complications are important in increasing the prolonged disability and high mortality of congestive heart failure The slowing of the circulation and the usually prolonged recumbency encourage the formation of thrombi in the heart or in the systemic or pulmonary veins with subsequent embolization Kinsey and White (71) reported the presence of pulmonary infarction in 21 of 50 cases of congestive heart failure studied at autopsy In a study of pulmonary embolism occurring in medical cases Carlotti Hardy Linton and White (72) found that the admission diagnosis was congestive heart failure in 104 of 273 cases

Cardiac patients may die of myocardial failure or of ventricular fibrillation but a large proportion of sudden deaths ascribed to these frequently unconfirmed diagnoses are actually the result of vascular occlusions unrecognized clinically

Paradoxical embolism though relatively uncommon is of interest in connection with systemic arterial embolization Thompson and Evans (73) reported varying degrees of patency of the foramen ovale in 35 per cent of 1 100 consecutive autopsies in 29 per cent the opening would admit a probe in 6 per cent a pencil They quoted Wittig who noted in 1927 that 50 per cent of instances of paradoxical embolism are preceded by pulmonary embolism The possible role of pulmonary embolism in increasing the pressure in the right atrium and so forcing embolic material through the valve flap of a patent foramen ovale has been discussed recently by Ross and Sprague (74)

cause for the embolism in 64 of 98 patients Rheumatic heart disease was responsible for the auricular fibrillation in about two thirds of the cases (in 41 instances) arteriosclerotic heart disease in 17 cases In one case fibrillation was associated with Pick s disease and in 5 cases the cause was undetermined Although it has been commonly believed that embolization is especially apt to occur when a fibrillating heart is reverted to a normal sinus rhythm either spontaneously or as a result of the administration of quinidine Warren and Linton were unable to establish this sequence of events in any of their patients

Rarely in cases of valvular stenosis with auricular fibrillation a ball thrombus is formed free in an auricular chamber This has been reported in more than 30 instances in the left auricle but there is only 1 unquestioned case report of a true ball thrombus in the right auricle This case was reported with a summary of the literature by Wright Flynn and Druet (68) Auricular thrombi sometime occur in mitral stenosis without auricular fibrillation and serve as the source of systemic emboli In a series of 72 cases of mitral stenosis complicated by cerebral embolism (69) 55 patients had auricular fibrillation One third of the entire group exhibited congestive heart failure and one third died immediately Pulmonary embolism with infarction is a common complication of mitral stenosis but is more often the sequel to thrombus formation in the leg veins and to congestive heart failure than to thrombus formation in the chambers of the right heart (70)

The chief complications of bacterial endocarditis whether acute or subacute are due to the infarction of various organs from emboli originating in intracardiac thromboses The spleen is one of the common sites of infarction but systemic emboli lodging in the brain the kidneys or extremities frequently produce more serious consequences Pulmonary infarction is not as common since the vegetations are generally or preponderantly on the left side of the heart It may occur in cases of congenital heart disease affecting the right side of the heart and complicated by an endocarditis Coronary emboli occur rarely Of especial interest are those cases of subacute bacterial endocarditis which

blood vessels outside of the heart and these may in some cases produce more serious consequences than do the original coronary occlusions

In a series assembled from the literature 11 5 per cent of the patients had peripheral thromboembolic lesions clinically (77) However as Barritt (78) has pointed out various reports in the literature have demonstrated that peripheral thromboembolic lesions are found in from 25 to 70 per cent of such cases at autopsy Since post mortem examinations frequently do not include thorough studies of the vessels of the extremities it is likely that the figures given in most reported series are incomplete

In the material studied by Hellerstein and Martin (77) 45 per cent of the 160 cases had a total of 111 peripheral thromboembolic lesions at autopsy In those cases in which mural thrombi were demonstrated peripheral thromboembolic lesions were found in 55 per cent but in those cases without mural thrombi peripheral thromboembolic lesions were found in only 39 per cent In contrast the incidence of peripheral vascular occlusions in one hundred cases selected at random from patients dying from causes other than myocardial infarction was only 15 per cent Peripheral thromboembolic lesions were an important cause of death (main cause and contributory cause) in 27 per cent of the 160 autopsied cases reported by Hellerstein and Martin and in 21 5 per cent of the 200 cases reported by Eppinger and Kennedy (79) Whereas there is *clinical evidence* of thrombophlebitis in only 1 8 per cent of patients during the period of recovery from an acute coronary occlusion with myocardial infarction there is evidence of thrombophlebitis *at autopsy* in 8 3 per cent of cases which die during this period (77)

Pulmonary emboli have been reported at autopsy as occurring in from 3 to 12 per cent of cases of coronary occlusion with myocardial infarction In a large combined series the incidence was 23 5 per cent It is an important cause of death in from 5 to 16 per cent of cases Pulmonary embolism was the main cause of death in 10 6 per cent of a large combined series (77) and the cause for sudden death in 6 5 per cent of the 200 cases reported by Eppinger and Kennedy (79) Among the patients in this series

CHAPTER 4

Thromboembolic Phenomena in Coronary Occlusion with Myocardial Infarction

THE most common complications of coronary occlusion with myocardial infarction are thromboembolic. These include thromboembolic complications within the heart itself and those which occur in the vascular system elsewhere in the body. Intracardiac thromboembolic complications include extensions of the initial coronary thrombus formation of new coronary thrombi in the same or in other coronary arteries and the formation of mural thrombi within the cardiac chambers. Mural thrombi give rise frequently to emboli which enter the systemic or pulmonary vessels.

Nay and Barnes (75) found that 15 per cent of the 100 cases of coronary occlusion with myocardial infarction analyzed by them had suffered a *clinically recognized* secondary myocardial infarction during the immediate convalescence from a previous infarction. Wartman and Hellerstein (76) found multiple infarcts in 41.3 per cent of 160 cases of myocardial infarction *studied at autopsy*. In 32 per cent of these autopsied cases there were both fresh and old infarcts, in 6 per cent there were *multiple recent infarcts* and in 3 per cent there were multiple old infarcts.

Mural thrombi are described in various reports as occurring in from 17 to 83 per cent of cases of myocardial infarction studied at autopsy. The tremendous variation in these figures is undoubtedly related in some degree to the care with which these thrombi are sought. Wartman and Hellerstein found mural thrombi in 10 per cent of their 160 cases, in 34 per cent of those patients who had experienced a single infarct and in 48.5 per cent of those in whom multiple infarcts had occurred.

In patients who have suffered a coronary occlusion recently thromboembolic lesions occur with considerable frequency in

location of peripheral thromboembolic lesions following myocardial infarction'

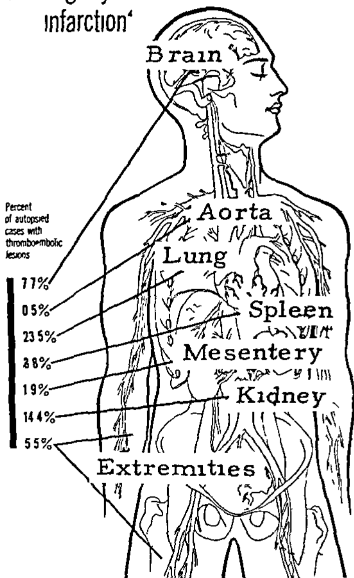


FIGURE 4B

FIGURES 4A AND B Copy of a side panel from the American Heart Association Exhibit Importance of Thromboembolic Complications Accompanying Myocardial Infarction as Reported in the Literature

IMPORTANCE OF THROMBOEMBOLIC COMPLICATIONS ACCOMPANYING MYOCARDIAL INFARCTION AS REPORTED IN THE LITERATURE

CARDIAC COMPLICATIONS

THE MOST COMMON CARDIAC COMPLICATIONS OF MYOCAR INFARCTION ARE THROMBOEMBOLIC

SECONDARY INFARCTS

[illegible][1]

[illegible][2]

[illegible] in 32%

[illegible] in 6%

[illegible] in 8%

MURAL THROMBI

At autopsy in 17% to 83%

At autopsy in 44% in a large com series

At autopsy in 40%[2]

After single infarcts in 34%

After multiple infarcts in 48 5%

PERIPHERAL COMPLICATIONS

PERIPHERAL THROMBOEMBOLIC LESIONS

[illegible] in a large combined series

[illegible] 70%[3]

[illegible]

With mural thrombi 55% Without mural thrombi 39%

Important cause of death in 27%[4] and 24 5%[5]

THROMBOPHLEBITIS OF THE LOWER EXTREMITIES

Clinically in 4 8% At autopsy in 8 3%

PULMONARY EMBOLISM

At autopsy up to 42%

At autopsy in 23 5% in a large combined series

Important cause of death in 5% to 46% of cases

Main cause of death in 10 6% in a large combined series

Cause of sudden death in 6 5% of 200 cases[5]

Important cause of death in 32 7% of those cases dying in congestiv failure

FIGURE 4 A See legend on following page

See legend on following page

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location of peripheral thromboembolic lesions following myocardial infarction[4]

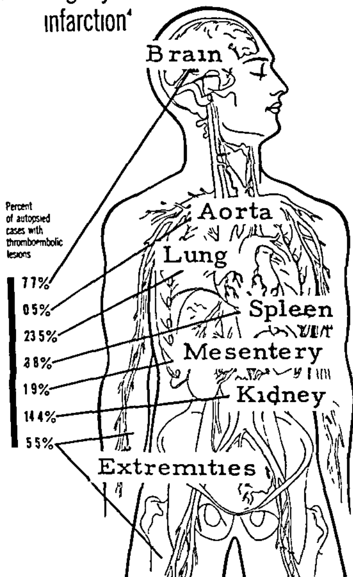


FIGURE 4B

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IMPORTANCE OF THROMBOEMBOLIC COMPLICATIONS ACCOMPANYING MYOCARDIAL INFARCTION AS REPORTED IN THE LITERATURE

CARDIAC COMPLICATIONS

THE MOST COMMON CARDIAC COMPLICATIONS OF MYOCARDIAL INFARCTION ARE THROMBOEMBOLIC

SECONDARY INFARCTS

- Clinically in 15[illegible] [1]
- At Autopsy in 11%[2]
  - Fresh and old in 32%
  - Multiple recent in 6%
  - Multiple old in 8%

MURAL THROMBI

- At autopsy in 17% to 83%
- At autopsy in 44% in a large combined series
- At autopsy in 40%[2]
  - After single infarcts in 34%
  - After multiple infarcts in 48 5%

PERIPHERAL COMPLICATIONS

PERIPHERAL THROMBOEMBOLIC LESIONS

- Clinically in 11 5% in a large combined series
- At autopsy in 25 to 70%[3]
- At autopsy in 45%[4]
  - With mural thrombi 55% — Without mural thrombi 39%
- Important cause of death in 27%[4] and 24 5%[5]

THROMBOPHLEBITIS OF THE LOWER EXTREMITIES

Clinically in 4 8% — At autopsy in 8 3%

PULMONARY EMBOLISM

- At autopsy up to 42 %
- At autopsy in [illegible]3 5% in a large combined series
- Important cause of death in 5% to 46% of cases
- Main cause of death in 10 6% in a large combined series
- Cause of sudden death in 6 5% of 200 cases[5]
- Important cause of death in 32 7% of those cases dying in congestive heart failure

FIGURE 4A See legend on following page

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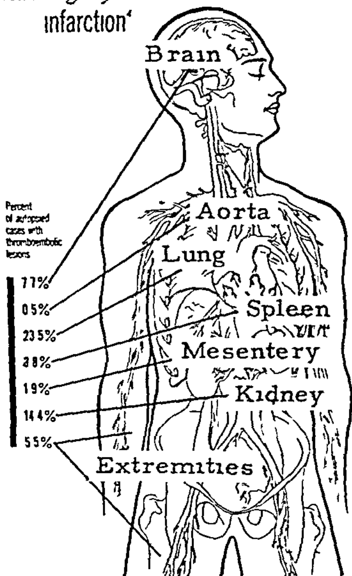


FIGURE 4B

FIGURES 4A AND B Copy of a side panel from the American Heart Associatio Exhibit Importance of Thromboembolic Complications Accompanying Myc cardial *Infarction as Reported in the Literature*

IMPORTANCE OF THROMBOEMBOLIC COMPLICATIONS ACCOMPANYING MYOCARDIAL INFARCTION AS REPORTED IN THE LITERATURE

CARDIAC COMPLICATIONS

THE MOST COMMON CARDIAC COMPLICATIONS OF MYOCARDIAL INFARCTION ARE THROMBOEMBOLIC

SECONDARY INFARCTS

- Clinically in 15%[1]
- At Autopsy in 41%
  - Fresh and old in 32%
  - Multiple recent in 6%
  - Multiple old in 3%

MURAL THROMBI

- At autopsy in 17% to 83%
- At autopsy in 44% in a large combined series
- At autopsy in 40%[2]
  - After single infarcts in 34%
  - After multiple infarcts in 48.5%

PERIPHERAL COMPLICATIONS

PERIPHERAL THROMBOEMBOLIC LESIONS

- Clinically in 11.5% in a large combined series
- At autopsy in 25% to 70%[3]
- At autopsy in 45%[4]
  - With mural thrombi 55% — Without mural thrombi 39%
- Important cause of death in 27%[4] and 24.5%[5]

THROMBOPHLEBITIS OF THE LOWER EXTREMITIES

- Clinically in 4.8% — At autopsy in 8.3%

PULMONARY EMBOLISM

- At autopsy up to 42%
- At autopsy in 23.5% in a large combined series
- Important cause of death in 5% to 46% of cases
- Main cause of death in 10.6% in a large combined series
- Cause of sudden death in 6.5% of 200 cases[5]
- Important cause of death in 32.7% of those cases dying in congestive heart failure[5]

FIGURE 4A See legend on following page

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Selzer (86) has recently pointed out that while myocardial necrosis and its sequellae determine to a large extent the immediate mortality following myocardial infarction the frequency of other secondary factors causing death indicates that the heart is not beyond repair in many patients who die following myocardial infarction

Selzer reviewed 95 cases of recent myocardial infarction with the idea of correlating the immediate sequellae with the prognosis in terms of mortality Twenty eight patients developed progressive circulatory failure either congestive failure or shock and at autopsy showed no important complication Twenty four patients died suddenly and at autopsy revealed no immediate cause of death other than infarction Thirty two patients died of complications demonstrable at autopsy and the clinical course and autopsy findings in these patients suggested that the advent of the complication had either turned the tide from possible recovery or at least accelerated death Thromboembolic complications in this category included 15 cases of embolism 6 cerebral 5 massive pulmonary 3 to the extremities and 1 mesenteric In a miscellaneous group 5 patients died of recurrent coronary occlusion during the first and second weeks after the initial myocardial infarction Thus 21 per cent of the patients died as a result of thromboembolic phenomena and 60 per cent of the cases had mural thrombi on the endocardium

At least 50 per cent of patients who died during the acute stage of infarction had evidence of effective circulatory compensation but died because of secondary complications a conservative estimate since all patients in shock or in heart failure were assumed to have irreversible cardiac damage

As Selzer states It appears then that from the standpoint of pathological changes and functional capacity of the myocardium death is preventable in a large proportion of patients who survive the initial attack of pain of myocardial infarction The prognosis of acute myocardial infarction is unpredictable because the importance of cardiac insufficiency—the direct consequence of the damage to the myocardium—is outweighed by secondary complications The immediate mortality is twice or perhaps three times greater than the estimated number of cases with irreparable

who died of congestive heart failure pulmonary embolism was an important cause of death in 32.7 per cent

In Hellerstein and Martin's material (77) the location of peripheral thromboembolic lesions expressed as per cent of autopsied cases with thromboembolic lesions was as follows brain 7.7% aorta including carotid vessels 0.5% lung 23.5% spleen 8.8% mesentery 1.9% kidneys 14.4% extremities 5.5%

Mintz and Katz (80) reviewed 572 cases of recent myocardial infarction observed at Michael Reese Hospital during the 5 year period 1940 to 1946 with particular attention to the factors leading to immediate mortality Only those deaths occurring during the patients stay in the hospital were considered and these occurred in 125 patients (a mortality rate of 21.9 per cent) Most of the patients were Jews since the hospital population of the Michael Reese Hospital is predominately Jewish A few were Negroes

Of the 52 patients (9.9 per cent) with thromboembolic phenomena recognized clinically 29 died (mortality rate of 55.8 per cent) Pulmonary embolism and cerebral embolism were by far the most common thromboembolic conditions reported and resulted in nearly all of the fatalities attributed to thromboembolism There were 26 pulmonary emboli with 14 deaths (mortality rate of 53.8 per cent) 11 cerebral emboli with 9 deaths (mortality rate of 81.8 per cent) and 2 patients with both pulmonary and cerebral emboli both of whom died One patient had a fatal mesenteric thrombosis

Of those patients who suffered thromboembolic complications 20 received digitalis and 16 of these died (mortality rate of 80 per cent) of the 32 who did not receive digitalis 13 died (mortality rate of 40.6 per cent) It may have been that the patients who received digitalis were among the more seriously ill but the authors caution that the observations of Macht (81) of deTakats Trump and Gilbert (82) and of Massie et al (83) indicating that digitalis promotes intravascular clotting though doubted by certain other observers (84 85) have not been disproved The two primary indications for digitalis congestive heart failure and auricular fibrillation in themselves predispose to thromboembolism Furthermore as Katz points out a real hazard of the use of digitalis is its tendency to produce ventricular fibrillation

SECTION II

THE MECHANISMS OF INTRAVASCULAR CLOTTING

cardiac damage The important sequellae of myocardial infarction which can be considered potentially preventable causes of death are serious arrythmias thromboembolic phenomena and shock

The great differences between the clinical and pathological figures for the incidence of thromboembolic complications are due to several factors among the more important of which are

(1) Patients who survive thromboembolic complications probably do not suffer as many or as severe episodes as patients who die from these complications and

(2) Autopsy clearly permits a more complete examination of the vascular system Figures based on clinical studies of thromboembolic complications almost invariably represent the minimal incidence of these complications and frequently constitute only a fraction of the thromboembolic phenomena actually present

*It must be recognized furthermore that in a very large propor*tion of autopsies performed in the past meticulous examination of all vessels particularly those of the pelvic viscera and lower extremities has not been the rule

CHAPTER 5

Current Concepts of Blood Coagulation

THERE are a number of factors which may induce the formation of an intravascular clot These include changes in the coagulability of the blood changes in the agglutinability of the platelets changes in the rate of blood flow and changes in the character and integrity of the vessel wall Sometimes one and at other times another of these factors plays the predominate role in initiating the development of a thrombus

The use of the anticoagulants to prevent and to treat thromboembolic phenomena has focused attention on the role which the formation of a fibrin clot by coagulation of the blood plays in the production of thrombi That increased coagulability of the blood is an essential cause for thrombosis is emphasized currently in contrast to the mechanistic view of the 19th and early 20th centuries that intravascular clots are built up primarily by the aggregation of platelets

Increased coagulability of the blood is undoubtedly an important factor in the formation of thrombi but some consideration must be given to the view expressed by Ludwig Aschoff who stated emphatically all histological research since the early work of Zahn Eberth and Schimmelbusch Welch and others speaks for the view that in human beings the occurrence of fibrin coagulation is not the first stage of thrombosis but that important changes in the morphological blood constituents precede it (87)

It is convenient to divide the process of blood coagulation into three phases for discussion as in Table III although this device is an oversimplification of the complex series of physico chemical reactions which occur In the initial phase of coagulation the plasma prothrombin is converted into thrombin in the presence of an adequate concentration of calcium ions and upon the addition to the plasma of a substance with thromboplastic activity This reaction occurs in vitro and in itself produces no visible

lated further that the linking of the two components through ionic calcium is a necessary prelude to the formation of thrombin. Quick contended that the progressive prolongation of the prothrombin clotting time of stored oxalated blood is not due to a diminution of prothrombin per se but is the result of the disappearance of the labile component A. He characterized component B as a factor which can be removed readily from oxalated plasma with aluminum hydroxide and which disappears from the plasma clinically in the hypoprothrombinemia due to vitamin K deficiency or to poisoning with dicumarol.

Quick (90-92) has subsequently abandoned the view that the 2 components are linked through ionic calcium and he has urged that the factor unstable in oxalated plasma be called the labile factor instead of component A. He has applied the latter term to the principle which is deficient in one type of congenital hypoprothrombinemia of which another type is presumably due to a deficiency of component B. A considerable body of opinion is critical of these interpretations (93-95).

The belief that prothrombin is a unitary principle has been defended ardently by Seegers and his associates (93, 94, 96) who utilize the two-stage method of Warner, Brinkhous and Smith (97) for determining the prothrombin concentration. These investigators, in a long series of studies, have found no evidence to support the theory that prothrombin is a complex, nor that prothrombin reacts stoichiometrically with thromboplastin to form thrombin. They believe that the circulating prothrombin in its native form reacts with thromboplastin and ionic calcium to form thrombin, but that the rate of this reaction in purified systems is ordinarily relatively slow.

Various observers have suggested that intravascular clotting is prevented ordinarily by the inhibition or antagonism of prothrombin by substances present normally in the blood, the so-called antiprothrombins, which must be neutralized before the prothrombin-calcium-thromboplastin reaction may proceed (95). The relatively slow rate of thrombin formation in purified systems might be explained, according to this theory, by the presence in such systems of small amounts of these natural inhibitors.

TABLE III

THE FUNDAMENTAL PHASES OF BLOOD COAGULATION IN VITRO

Phase	Physical Events	Chemical Events
1 Chemical Phase	During which no gross physical change is evident	Transformation of prothrombin into thrombin by the action of thromboplastin and calcium
2 Coagulation phase	By which the blood acquires the consistency of a gel	Transformation of fibrinogen into fibrin by the action of thrombin
3 Contraction Phase*	During which the clot shrinks and expresses serum	

* This phase is frequently ignored in descriptions of blood coagulation although it is of importance in the evolution of the final and relatively stable clot

physical change It is assumed that it also occurs in vivo In the second phase the plasma fibrinogen is transformed by the action of thrombin into the relatively insoluble fibrin the gelatinous blood clot Finally during the stage of contraction the clot shrinks and serum is expressed

The essential facts so stated are stripped of controversial detail and furnish a framework into which the majority of theories of blood coagulation may be fitted readily It must be realized however that each stage of the process is more complex than described and that in all probability the various reactions involved are in progress at the same time when clotting occurs

Prothrombin

Originally it was believed that the conversion of prothrombin into thrombin is a simple and direct stoichiometrical reaction A J Quick (88) using the one stage method of determining the plasma prothrombin clotting time subsequently identified with his name (89) presented evidence in 1943 that prothrombin is composed of ionic calcium and of 2 components designated as A and B which ordinarily circulate in the plasma He postu

lated further that the linking of the two components through ionic calcium is a necessary prelude to the formation of thrombin Quick contended that the progressive prolongation of the prothrombin clotting time of stored oxalated blood is not due to a diminution of prothrombin per se but is the result of the disappearance of the labile component A He characterized component B as a factor which can be removed readily from oxalated plasma with aluminum hydroxide and which disappears from the plasma clinically in the hypoprothrombinemia due to vitamin K deficiency or to poisoning with dicumarol

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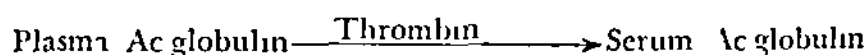
The belief that prothrombin is a unitary principle has been defended ardently by Seegers and his associates (93 94 96) who utilize the two stage method of Warner Brinkhous and Smith (97) for determining the prothrombin concentration These investigators in a long series of studies have found no evidence to support the theory that prothrombin is a complex nor that prothrombin reacts stoichiometrically with thromboplastin to form thrombin They believe that the circulating prothrombin in its native form reacts with thromboplastin and ionic calcium to form thrombin but that the rate of this reaction in purified systems is ordinarily relatively slow

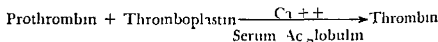
Various observers have suggested that intravascular clotting is prevented ordinarily by the inhibition or antagonism of prothrombin by substances present normally in the blood the so called antiprothrombins which must be neutralized before the prothrombin calcium thromboplastin reaction may proceed (95) The relatively slow rate of thrombin formation in purified systems might be explained according to this theory by the presence in such systems of small amounts of these natural inhibitors

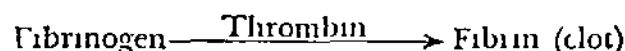
Accelerator Globulin

However Fantl and Nance (98 100) have demonstrated more recently the presence in the blood plasma of an independent factor which accelerates the activation of purified prothrombin by thromboplastin Their work has been confirmed and extended by Seegers and his associates (101 106 96) who postulate that this substance which they have called plasma Ac globulin is a proenzyme which is converted into serum Ac globulin by the action of small amounts of thrombin Serum Ac globulin and ionic calcium then catalyze the interaction of prothrombin and thromboplastin to form additional amounts of thrombin Seegers locates the action of Ac globulin in the blood clotting mechanism by the following equations









Seegers believes that these factors plasma Ac globulin and serum Ac globulin are identical with those described by Owren (107 108) as Factors V and VI

It must be recognized that differences in methodology may explain to some degree at least the differences in opinion among workers in the field of blood coagulation Thus A J Quick uses the one stage method for determining the prothrombin clotting time in his experimental studies while other workers have used the two stage method of Warner Brinkhous and Smith to demonstrate the accelerator factors the so called Ac globulins

The presence of ionic calcium is necessary for the coagulation of blood except under special experimental conditions Ordinarily the concentration of ionic calcium circulating normally in the blood is roughly optimal for the process of blood coagulation and clinically neither hypocalcinemia (tetany) nor hypercalcinemia modify the coagulation process in vivo Evidence has

been presented however that when a marked hypoprothrombinemia is induced by dicumarol the normal concentration of calcium in the blood is not sufficient for maximum prothrombin activity (109 111)

Thromboplastin

The participation of substances with thromboplastic activity in the process of blood coagulation is also more complex than has been thought previously It was demonstrated originally that extracts of a variety of organs possess thromboplastic activity—lung brain testicle ovary thymus etc and that the potency of these extracts depends largely upon their content of certain cephalin protein complexes There are also a variety of substances of diverse chemical nature which can induce the formation of a blood coagulum in vitro although acting by processes unrelated to the natural process of coagulation Among such agents are ninhydrin papain and tryptases obtained from soy beans and from pancreas

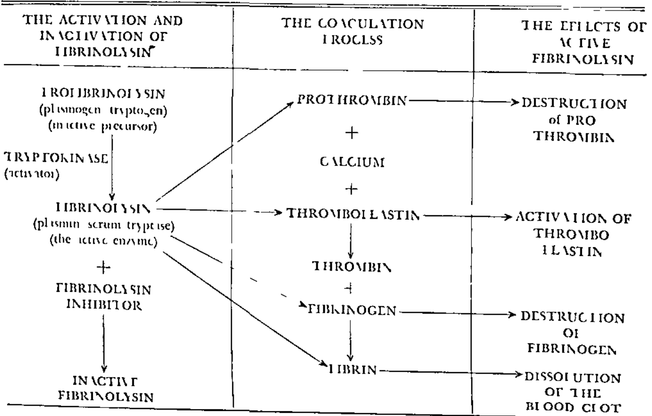
Ferguson (112 113) has suggested that before thromboplastin from the tissues or from disintegrating blood platelets can participate in the coagulation process it must be activated by serum tryptase (fibrinolysin plasmin) a proteolytic enzyme which circulates normally in the plasma in the form of a precursor (tryptogen profibrinolysin plasmogen) The complexity of modern concepts of coagulation are demonstrated by the multiplicity of interactions which have been suggested for fibrinolysin as outlined in Table IV

The time honored concept that the disintegration of the platelets is a dominant factor in the release of thromboplastin into the circulation has been challenged by the observation that coagulation can take place when few or no platelets are present in the blood However A J Quick (114) has stated that he does not believe that blood can clot if all of the platelets have been removed and cites his own work (115) and that of Seegers and Brinkhous that when the platelets are removed from the blood there is almost no consumption of prothrombin

To explain why the circulating blood remains fluid in the intact vascular system it was first assumed that thromboplastic substances are either not present in the blood or that they are present

TABLE IV

SUGGESTED INTERACTIONS OF FIBRINOLYSIN IN THE PROCESS OF BLOOD COAGULATION



in amounts inadequate to induce clotting This assumption was modified later by Tocantins and others to account for the possibility that relatively small amounts of thromboplastic substances might exist in the circulating blood They assumed that the blood must contain natural anticoagulants (antiprothrombins and antithrombins) and that coagulation cannot proceed until thromboplastic substances are present in excess Substances which have been suggested for this role of natural anticoagulant include heparin and by reason of their antiprothrombin activity fibrinolysin and thrombin That such natural anticoagulants do exist in the circulating blood in amounts sufficient to perform this function is unproved

Tocantins (116) has sought a possible thromboplastin inhibitor and has found a lipid substance which possesses very powerful antithromboplastin activity During the course of investigations on the chemical composition of thromboplastin Overman and Wright (117 118) have isolated a material possessing inhibitory powers by the chemical fractionation of thromboplastins prepared from dried beef brain and from rabbit lung The most active inhibitory fraction has chemical properties which are identical with those of inositol phosphatides obtained from brain and from soy bean This material is extremely potent in prolonging the plasma prothrombin time of normal human plasma and the coagulation time of normal whole blood Whether this fraction or some similar substance plays an important role in the process of blood coagulation in vivo has not as yet been determined

Fibrinogen

Fibrinogen is a plasma protein which is converted into fibrin in vivo by the action of thrombin The rapidity with which blood coagulates when a potent thrombin is added to it in even minute amounts suggests that an active thrombin is not normally present in the circulating blood Lyons (119 120) has presented evidence that the conversion of the circulating fibrinogen into fibrin is accomplished in two stages According to his views fibrinogen A the fibrinogen normally present in plasma is converted into fibrinogen B not normally in the plasma only in the presence of thrombin or in certain abnormal states (120) He has reported that

he is able to demonstrate fibrinogen B almost always in the blood of patients suffering from a variety of clinical disorders in which there is some degree of tissue necrosis and particularly when there is a pyogenic infection This work requires confirmation before it can be accepted generally

Cases of afibrinogenemia studied by MacFarlane (121) and by Pinninger and Prunty (122) are clinical curiosities in which fibrinogen is absent from the blood of these patients from birth Their coagulation times and prothrombin clotting times were prolonged infinitely the bleeding times were normal at the time of study and the patients themselves enjoyed good health

The process of blood coagulation involves multiple reactions between a variety of relatively complex colloidal substances and these reactions are influenced by a variety of factors such as temperature hydrogen ion concentration concentration of electrolytes and of specific coagulation factors and such colloidal phenomena as adsorption

A number of factors accelerate coagulation Thus clotting is more rapid at body temperature than at room temperature A foreign surface such as glass or damaged tissue accelerates clotting Tissue extracts from various organs can reduce the clotting time from *minutes to seconds Certain foreign* substances of a biological nature such as certain snake venoms accelerate clotting

Other factors retard or prevent clotting Low temperatures and certain surfaces for example those presented by paraffin collodion and certain plastics retard in vitro clotting The surface presented by the endothelium of the blood vessels undoubtedly plays an important role in maintaining the fluidity of the blood within the vascular system A high concentration of certain salts such as magnesium sulfate and sodium chloride likewise retards coagulation as do certain tissue extracts containing heparin

It is not to be wondered that the conclusions reached by various observers have varied widely and that as Ferguson has remarked careful appraisal of any experimental procedure in this field is essential to the evaluation and interpretation of the results obtained

CHAPTER 6

The Morphological Structure of Thrombi (87, 123-126)

ZAHN and Eberth and Schimmelbusch showed that an accumulation of the blood platelets and leucocytes constitutes the first material laid down in the process of building the white portion of a thrombus Welch showed subsequently that in a completely finished thrombus the variations in color are perfectly regular The first part of the thrombus is chiefly white in color the middle part is mixed in color and the distal and final portion is a deep red

It is worth noting with Aschoff that the white thrombus may be of the smallest possible size and extent whereas the final red portion often forms the bulk of the thrombus Furthermore a structure of the sort seen in the white thrombus is the only certain sign microscopically by which we can recognize the anti mortem nature of a thrombus (87)

It is clear that the accumulation of blood platelets typical of a platelet thrombus can occur only when the blood is circulating Solid elements are taken from the blood stream and laid down in the form of a framework of specially situated lamellae So long as the blood flows through the framework new masses of blood platelets are laid down to build up new systems of lamellae behind the first The original system naturally grows progressively faster and the openings between the lamellae are progressively narrowed Finally the flow of blood between the lamellae is brought to a complete standstill completing the primary thrombus since no more blood platelets are carried past and hence further growth becomes impossible

The chemical or physico chemical properties which permit masses of platelets to aggregate so readily is not known How important is the number of platelets circulating in the blood stream is not clear but it may be supposed that the increased tendency to

ward thrombosis following blood loss may be aggravated by the increase in circulating platelets

Eberth and Schimmelbusch found that when the blood stream is slow the white corpuscles being of lighter specific gravity than the erythrocytes tend to travel at the margins of the blood stream in close proximity to the vessel wall As the growing system of platelets forms a thrombus the main blood stream is divided up into a series of smaller streamlets and as the slowing of the blood stream occurs the leucocytes are found in close proximity to the framework of platelets to which they become attached

When the blood stream is sufficiently obstructed by this white thrombus the whole column of blood peripheral to this point and to the next anastomosing vessel becomes stationary and undergoes a very rapid and complete coagulation to become the red thrombus Though the denser portion of this red thrombus in the neighborhood of the white thrombus is rich in fibrin and leucocytes and gives an occasional suggestion of lamellae formation peripherally it is spongy and semi fluid and the structure of the mass more nearly approaches that of normal blood

In the red thrombus there is no definite framework of platelets which are either completely absent or occur only infrequently This red thrombus microscopically resembles a postmortem clot and consists of irregular masses of red blood cells white blood cells fibrin and platelets The process of coagulation of this blood is undoubtedly the result of the liberation of relatively large amounts of thromboplastic substance from the numerous agglutinating platelets of the white thrombus and from other tissues as well Perhaps as Aschoff concluded the agglutination (of blood platelets) is so to speak only a means of creating in the circulating blood conditions which are necessary to allow the crystallizing out of fibrin a process *which cannot occur in the* circulating blood under ordinary conditions (87)

Thus the white thrombus and the red thrombus are essentially different depending on the fact that the white thrombus is formed in a flowing stream of blood the red thrombus in stationary blood They are connected by an intermediate zone which is more or less mixed in character The blood stream must flow more slowly or differently from the way it did previously in order

to produce white thrombi Physical principles studied in streams suggest the importance of the role of eddies and cross currents in the production of these thrombi

In the arterial system changes must be very striking to produce such slowing In the venous system however there are a number of factors which can readily account for the slowing of the blood and the formation of eddies in the blood The locations and anatomic relations of the veins in the leg the proximal portion of the femoral veins and the pelvic veins predispose to interference with blood flow

There are four conditions common to most veins even though undiseased which may predispose to thrombus formation

(1) The continued pressure on the walls of a vein resulting from the force of gravity or from other prolonged and severe extrinsic forces such as a gravid uterus excessively tight girdle etc which leads to widening of the vessel and to the slowing of the blood stream

(2) The widening of vessels at those points around the valves at which the musculature of the venous wall is notoriously deficient

(3) The possibility of a backward pulsation in the veins the so called venous pulse which is often most marked in the proximal portion of the femoral vein and

(4) The angulation and kinking of certain vessels and pressure from extraneous structures on the wall of the veins when the body is in the prone position

One or several of these factors may be involved in the development of an intravascular clot by slowing the blood stream and permitting platelets to be deposited on the walls of the vessels to form the so called agglutination thrombus

Alterations in the character of the wall of very large blood vessels must be a limited factor in the production of thrombosis as illustrated in the highly atherosclerotic aorta where even the most advanced changes frequently do not lead to thrombosis There is of course no slowing of the blood stream by the atheromatous changes in so large a vessel In smaller arteries this factor is more important Fatty changes in the endothelium of veins do not in themselves play an important role in the formation of thrombi and severe phlebosclerotic changes are rarely a contributing factor

In brief though slowing of the blood stream and alterations in the condition of the platelets are directly responsible for thrombus formation changes in the walls of the vessels alterations in cardiac action and loss of blood are significant contributory factors

The two phenomena agglutination and coagulation are genetically different and each can occur without the other (123) In the case of ordinary thrombosis the two processes are closely related and the agglutination process is the indirect cause for the coagulation process Whereas the former can be brought about readily the latter is difficult to induce Stopping the blood stream will not alone suffice The introduction of large amounts of thromboplastin into the flowing blood will produce a coagulation thrombosis but ordinarily the important factors in its production in vivo are stagnation of the blood stream and an increase in liberated thromboplastin

Blood Platelets

Recent studies of the blood platelets have been directed largely in two directions There have been investigations of the variations in the number of circulating platelets in health and disease There have also been numerous studies to determine variations in the quality of platelet adhesiveness These have for the most part utilized the method first described by H P Wright (127) whose original findings were confirmed by Spooner and Meyer (128) Weiner Zeltmacher Reich and Shapiro (129) have recently reported instances of hemorrhagic phenomena in which a diminished adhesiveness of the platelets was the only defect discovered in the coagulation mechanism These authors state that the adhesiveness of platelets is reduced in the presence of hypocoagulable blood but that it may or may not be enhanced when the blood is hypercoagulable

There is as yet no general agreement as to the explanation for this quality of platelet adhesiveness The possible role of increased platelet adhesiveness in the production of multiple platelet thromboses of the capillaries arterioles and venules (thrombotic thrombocytopenic purpura) is unexplored as far as we know (130 131)

SECTION III

RATIONALE FOR THE USE OF THE ANTICOAGULANTS

vascular thrombi produced artificially by mechanical or chemical means (31)

Murray Jaques Perrett and Best (139 140) first showed that the thrombi which form ordinarily on the intimal surfaces of veins which have been traumatized by mechanical or chemical means can be prevented completely by the administration of adequate amounts of purified heparin before and for prolonged periods following the injury When heparinization was continued for at least 3 days following the injury the traumatized veins were completely healed and there was no indication that thrombi would form subsequently at the site of injury

Best Cowan and MacLean (141) then studied the formation of white thrombi in shunts composed of glass or cellophane tubing inserted between an artery and a vein in anesthetized laboratory animals They found that the formation of large white thrombi can be prevented delayed or at least inhibited when large amounts of heparin are administered although the concentration of heparin was necessarily higher in experiments in which glass tubes were interposed in the vessels than when thrombus formation was prevented strictly in vivo

Solandt and Best (142) devised a method whereby coronary thrombosis can be produced regularly in experimental animals by isolating a coronary artery and injecting into it a solution of sodium ricinoleate which is retained in contact with the intima for 5 minutes before the clamps on the vessel are released A thrombus forms in almost every instance in which no heparin is used When the animals are heparinized however thrombus formation is an exceedingly rare occurrence

Finally Solandt Nassim and Best (143) devised a method whereby a large mural thrombus can be produced regularly in the left ventricle by ligating the anterior descending branch of the left coronary artery and then injecting sodium ricinoleate into the myocardium just beneath the endocardium When heparin is not administered to the animal there is consistently a rapid formation of mural thrombi When heparin is given well before the experiment no mural thrombi are formed Solandt and Best (144) showed later that large doses of heparin must be administered over considerably longer periods of time to manifest an inhibi

tory effect on the agglutination of platelets than to produce a prolongation of the clotting time

Curiously many commercial preparations of heparin will cause agglutination of platelets in vitro and in vivo (145) although this phenomenon may be due to the fact that heterologous heparin has been used in the experiments It is also possible that the agglutination of platelets by heparin is due to the presence in the heparin preparations of an impurity (146)

Heparin and Sludged Blood

Laufman Martin and Tanturi (147) have recently issued a preliminary report of their studies on the formation of sludge in the small vessels of the dog following acute temporary occlusion of the larger veins They found in over 70 instances where the portal vein or the superior mesenteric vein was occluded in normal dogs that the formation of sludge could be observed in the small peripheral mesenteric veins within 10 to 20 minutes following occlusion As the blood stream continued to slow thrombi were noted in some of the vessels especially the capillaries and venules usually within 30 minutes after the appearance of the sludge The groups of agglutinated cells attached themselves to the endothelial lining of the vessels more cells became attached to the mass and a thrombus formed which obliterated the entire lumen as the blood flow ceased entirely When the clamp was released after approximately 1 hour the flow had either ceased completely or was in the ebbing stage in most small vessels A resumption of flow washed many vessels free of agglutinated cells but in some vessels thrombosis persisted

They concluded that thrombosis in these small vessels consisted of 4 stages

(1) The formation of sludge

(2) The adherence of the sludged masses to the endothelium

(3) The aggregation of more cells to the agglutinated mass and

(4) The complete cessation of flow through the involved vessel when it had become entirely occluded by the agglutinated mass

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CHAPTER 8

Dicumarol and Experimental Thrombosis

Dicumarol and the Coagulation Time of Whole Blood

DICUMAROL when administered orally to animals or to man produces a prolongation of the prothrombin clotting time of the blood plasma It does not in the doses commonly used therapeutically prolong the coagulation time of the whole blood as measured in glass tubes by the tests ordinarily employed (148) This point has been raised frequently in the past as evidence that dicumarol on theoretical grounds at least should not be an effective anticoagulant clinically This basis for criticism is simply not valid In the first place one is not justified in accepting the notoriously crude in vitro test for the coagulation time of the whole blood as a criterion against which to assess the effectiveness of dicumarol

As Eagle has pointed out (149) Numerous methods have been suggested for measuring the coagulability of the blood Although the simplest procedure is to measure the coagulation time this determination is of questionable significance Not only is it markedly affected by such adventitious factors as temperature shaking the diameter of the tube and its cleanliness but the results are at best difficult to evaluate A significantly retarded coagulation time clearly indicates that something is amiss but offers no clue as to the factor at fault This may be a qualitative or quantitative deficiency in prothrombin fibrinogen or platelets or an undue increase in antithrombin or some heparin like factor A normal coagulation time on the other hand offers no assurance that the coagulation mechanism is in fact normal Thus the normal blood fibrinogen thromboplastin or prothrombin content is enormously in excess of that actually required for coagulation and a significant diminution of any one of these factors may be associated with a coagulation time which falls within normal time limits

When heparin in doses of 6 to 10 mg was injected intravenously into dogs weighing about 5 kg after sludge formation had been produced by venous occlusion there was no alteration in the appearance of the sludge but the clumps of sludged cells did not become adherent to the vessel wall as readily as did those in the control animals The clumps of massed cells moved with the flow of the blood stream and when the clamps were removed from the larger vessels the blood resumed a completely free flow in all vessels observed No residual thrombosis was observed When heparin was injected intravenously in doses of from 5 to 10 mg before the veins were occluded sludge again formed in from 9 to 35 minutes following occlusion but the complete arrest of the stream was considerably delayed when compared with controls

Whereas in the controls the majority of vessels were filled with masses of adherent and agglutinated cells within 30 minutes in the animals heparinized prior to venous occlusion there was complete agglutination in only 1 dog after 45 minutes In all other heparinized animals the sludged clumps of cells did not adhere to the endothelium and were promptly washed away when the occluding clamp was removed It thus appears that the administration of heparin in clinically therapeutic doses has no effect on the formation of sludge It does however effectively prevent the formation of thrombi from aggregates of sludged cells

Heparin and Platelet Adhesiveness

H P Wright (127) has demonstrated that the adhesiveness of blood platelets is diminished in vitro by the addition to blood samples of various anticoagulant substances including heparin The adhesiveness is reduced proportionately as the concentration of the anticoagulant is increased and the rate of removal of the platelets from rotated blood is independent of the mode of action of the anticoagulant whether heparin sodium oxalate or chlorazol dyes were used

time of the blood of subjects to whom dicumarol has been administered in therapeutic amounts is greatly prolonged

Thus Davidson and MacDonald (148) found that the coagulation time of *patients to whom dicumarol had been administered* was far more prolonged when determined in lusteroid tubes than when determined in glass tubes although the variability in results was also greater Prolongation of the coagulation time was also frequently detected as much as a day earlier in lusteroid tubes than in glass They suggested that the coagulation time in lusteroid tubes indicates the true coagulation defect more closely than does glass

Moloney and his associates (151) using glassware coated with a silicone (drifilm) after the method described by Jaques and his coworkers (152) have demonstrated that the administration of dicumarol does prolong the coagulation time of whole blood in drifilmed tubes even when similar results cannot be obtained in plain glass tubes Paraffin collodion and plastics such as lusteroid have been used repeatedly in the past to simulate more closely endothelial surfaces (153 154)

Experimental Intravascular Thrombosis

Bingham Meyer and Pohle (39) were originally unsuccessful in their attempt to study the effect of dicumarol on the formation of intravascular thrombi Dale and Jaques (155) however produced intravascular thrombi in dogs by crushing the radial or saphenous veins on a linen thread by the method of Murray et al (139 140) and extracorporeal thrombi in glass cells after the method of Best Cowan and MacLean (141) In both series of experiments when dicumarol was administered to the dogs (in a single dose of 10 mg /kg intravenously 60 hours previously) the incidence of thrombus formation was reduced sharply Platelet counts demonstrated no significant change from the normal

Richards and Cortell (156) utilized the chemical method of Murray et al (139) for producing thrombosis in the peripheral veins of dogs by the injection of ethanolamine oleate When the animals were injected with the chemical from 3 to 5 days after the initiation of dicumarol therapy the incidence and degree of thrombus formation was greatly reduced Bollman and Preston

A J Quick (150) states that the determination of the coagulation time of the blood is among the most empirical procedures routinely employed in the clinical laboratory and is one most *prone to be misinterpreted* He concludes from his own observations and from a study of the literature that it becomes clear that the coagulation time has limited value in the study of the known hemorrhagic diseases The coagulation time is a measurement of the intrinsic power of the blood to convert fibrinogen to fibrin It is an empirical test no matter how performed and therefore in order to be reliable requires that the test be done on venous blood under strictly controlled conditions The coagulation time is prolonged in hemophilia hypoprothrombinemia afibrinogenemia and heparinemia In hemophilia the coagulation time theoretically is a measure of the severity of the disease but practically is of limited value since the coagulation time may be within normal limits in some patients the prothrombin consumed in the coagulation of hemophilic blood is there*fore a better guide for diagnosis* The coagulation time in hypoprothrombinemia is relatively little prolonged until a drastic reduction occurs The test is therefore of no value for establishing a hemorrhagic condition in hypoprothrombinemia In afibrinogenemia the blood is incoagulable A small amount of fibrinogen restores the coagulation time to normal The presence of heparin increases the coagulation time The test is therefore useful in controlling the therapeutic action of this drug

While the administration of dicumarol in ordinary doses does not influence the coagulation time of the whole blood as determined by the commonly employed techniques it does prolong the coagulation time of the whole blood under certain circumstances It is well established for instance that when the prothrombin clotting time of the plasma is markedly prolonged as following the administration of large doses of dicumarol the coagulation time of the whole blood is likewise prolonged (148)

Clotting in Lusteroid and Silicon Tubes

Of greater significance however is the fact that if the coagulation time of the whole blood is determined in lusteroid or dri filmed tubes instead of in ordinary glass tubes the coagulation

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of the occlusion a rapid flow of blood was resumed in all of the small vessels

Dicumerol and Platelets

Baronofsky and Quick (158) reported that the platelets of blood obtained from animals whose prothrombin level has been drastically reduced by feeding dicumarol show no tendency to agglutinate in the absence of an anticoagulant Spooner and Meyer (128) confirmed the observation previously reported by Wright and Prandoni (42) and by Dale and Jaques (155) that dicumarol has no effect on the actual platelet count Spooner and Meyer (128) and H P Wright (159) have shown that when dicumarol is administered orally to experimental animals it decreases the adhesiveness of the platelets as determined by the method of H P Wright (127)

Experimental Coronary Occlusion

Experiments duplicating those performed by Best and his associates producing coronary thrombosis by chemical means and mural thrombosis by combined chemical and mechanical means and then determining the effect of heparin in reducing the incidence of thrombi have not been carried out using dicumarol as the anticoagulant as far as we are aware There are however studies which are of considerable interest in this connection

Blumgart and his coworkers (160 161) produced experimental myocardial infarction in dogs by ligating the left anterior descending coronary artery To some of these animals dicumarol or heparin and dicumarol were administered immediately postoperatively to determine if adverse myocardial changes might result from anticoagulant therapy

Dicumarol was administered to the dogs in doses designed to maintain the prothrombin clotting time between 20 and 30 seconds Since the average prothrombin clotting time in normal dogs was 8 8 ± 1 1 seconds this range represented a reduction in prothrombin activity to between 20 and 12 per cent of normal The usual dosage schedule was 50 mg of dicumarol by mouth on the day of operation and 50 mg on the first postoperative day

(41) found that when glass cannulas were placed in the carotid and femoral arteries of normal dogs the great majority of the cannulas thrombosed completely within 20 minutes When the animals were dicumarolized (prothrombin times greater than 30 seconds normal values for canine blood 9 to 10 seconds) the cannulas remained patent for 6 to 8 hours at which time the experiments were terminated They found that cannulas of glass and of metal which rapidly thrombose in the blood vessels of normal dogs remain patent in dicumarolized dogs during the course of physiological experiments lasting 6 and 8 hours

Thill Stafford Spooner and Meyer (157) repeated the experiments of Richards and Cortell (156) using monoethanolamine oleate as a chemical irritant and confirmed the fact that the incidence of thrombus formation was definitely reduced in animals whose prothrombin times were prolonged from 2 to 7½ times the normal

These experiments established the fact that there is an effective reduction in the formation of intravascular and of extracorporeal (glass cannulas) thrombi when the prothrombin clotting time is markedly prolonged by the oral administration of dicumarol

Dicumarol and Sludged Blood

The experiments referred to above have been criticized on the basis that the amounts of dicumarol used and the prothrombin times maintained in the experimental animals had in the majority of instances been in excess of those ordinarily employed clinically in man Of particular interest therefore is the experience of Laufman et al (147) In their experiments previously referred to in chapter 7 6 dogs were given doses of dicumarol (from 25 to 50 mg per day for 3 days) so that just prior to the venous occlusion the prothrombin levels on diluted plasma ranged from 15 to 25 per cent of normal the usual therapeutic level in man Sludge appeared within 1 to 30 minutes and the appearance of the blood flow after 1 hour was no different from that observed in the heparinized animals Contrary to the findings in the control animals the sludged masses did not adhere to the intima and in no instance was there any thrombus formation Upon release

changes in the dicumarolized dogs as compared with the controls

The authors concluded that the experiments give no evidence that dicumarol has a favorable effect on the evolution or outcome of *established* experimental myocardial infarction They recognize that their results can hardly be compared to those anticipated in clinical coronary occlusion since their animals had healthy coronary circulations the occlusion by ligation was both sudden and complete and the number of experiments were too few for statistical analysis Their conclusions can hardly be applied to coronary occlusion with myocardial infarction in man since the use of anticoagulants clinically is directed primarily to the prevention of thromboembolic phenomena and should not be expected to alter the normal evolution of an existing myocardial infarct

LeRoy and Nalefsky (163) have produced experimental myocardial infarction by ligating the anterior descending branch of the left coronary artery with the purpose of determining if the use of dicumarol might lead to adverse myocardial changes Their results confirming those described above indicate that it does not

Since in animals permitted to survive for a week or more the prothrombin time fell toward normal on the 6th or 7th days additional doses of 20 to 50 mg of dicumarol were administered to these animals

The animals were sacrificed at various intervals postoperatively and detailed gross and microscopic examinations were performed on each heart Fifteen dogs who did not receive anticoagulants served as a control group Fourteen animals received dicumarol only and 3 also received heparin for several hours postoperatively until the effect of dicumarol was apparent

The incidence and magnitude of hemorrhagic extravasations on the endocardium and pericardium were the same in the treated and untreated groups The incidence and magnitude of miliary hemorrhages on microscopic examination of the myocardium were similar in the dicumarolized and in the control animals In the few dogs to whom sufficient dicumarol was administered to elevate the prothrombin time to levels as high as 132 seconds no increase in hemorrhagic phenomena were observed in the myocardium The size of the infarcts produced and the rate and character of healing did not differ between the treated and control groups Thrombotic occlusions of the smaller arteries within the infarcted areas were as common in dicumarolized animals as in the controls No mural thrombi were found in either treated or untreated dogs The development of collateral anastomoses between the coronary arteries was the same in both groups

The authors concluded that dicumarol produces no adverse effect on the myocardium of dogs nor does it retard the healing or the development of collateral circulation in experimentally produced myocardial infarction

Beattie et al (162) determined the effect upon experimental coronary occlusion produced by ligation of the anterior descending branch of the left coronary artery of dicumarol therapy begun after the artery had been ligated Dicumarol was given in doses of 5 mg /kg by gavage while the animal was still anesthetized and an attempt was made to maintain the prothrombin time between 10 and 30 per cent of normal although considerable difficulty was encountered in maintaining this level There was no striking difference in the electrocardiographic or pathological

changes in the dicumarolized dogs as compared with the controls

The authors concluded that the experiments give no evidence that dicumarol has a favorable effect on the evolution or outcome of *established* experimental myocardial infarction They recognize that their results can hardly be compared to those anticipated in clinical coronary occlusion since their animals had healthy coronary circulations the occlusion by ligation was both sudden and complete and the number of experiments were too few for statistical analysis Their conclusions can hardly be applied to coronary occlusion with myocardial infarction in man since the use of anticoagulants clinically is directed primarily to the prevention of thromboembolic phenomena and should not be expected to alter the normal evolution of an existing myocardial infarct

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SECTION IV

THE USE OF THE ANTICOAGULANTS CLINICALLY

CHAPTER 9

Indications for the Use of the Anticoagulants

IT MUST be clearly understood that the action of the anti coagulants is primarily prophylactic to prevent or to retard the formation of intravascular thrombi and consequently to minimize also the hazard of embolization The use of the anti coagulants in the treatment of existing thromboembolic lesions is based likewise on the ability of these drugs to prevent or to minimize the occurrence of further thromboembolic complications whether extensions of the existing process or new thromboembolic lesions elsewhere in the body

There is some evidence largely clinical that the anticoagulants do modify the natural evolution of thromboembolic lesions but it is difficult to prove that this action is not merely to prevent the accretion of additional thrombus to the existing lesion during the course of the latter s development For example it has been reported that retinal hemorrhages complicating retinal venous thrombosis resolve more rapidly under anticoagulant therapy than without Likewise it has been claimed that mural thrombi complicating coronary occlusion with myocardial infarction tend to be smaller more regular in outline and smoother on the surface in cases treated with anticoagulants than in those untreated However the hastening of resolution and the altered character of the lesion if confirmed may represent only an inhibition of progressive thrombus formation and not a modification of the evolution of the primary thromboembolic lesion

It has been suggested that anticoagulant therapy may promote the absorption of clots and may hasten the resolution of thrombi At the present time this is purely speculative Before such a conclusion is reached with certainty it will be necessary to demonstrate that there is not only an accelerated recovery when anti coagulants are used but that such acceleration is due to an effect on the existing intravascular clot and not to the prevention of its

propagation It is possible that there are fibrinolytic enzymes in the blood (e g fibrinolysin) which assist the resolution of thrombi by lytic action Anticoagulants would favor such action by preventing the simultaneous development of additional thrombus Unfortunately current knowledge concerning these enzymes is not only meager but is based entirely upon their action in vitro

There are certain well defined and quite generally accepted indications for the use of the anticoagulants (164) There are also certain conditions in which the use of the anticoagulants has been reported favorably but not as yet with sufficient evidence to warrant unreserved recommendation Finally anticoagulants are being tried on a limited scale in certain diseases for which on theoretical grounds they may be of value The indications for and possible uses of anticoagulant therapy are enumerated in Table V The use of the anticoagulants in these various conditions is discussed in the following sections

(1) PULMONARY EMBOLISM

Anticoagulants should be administered immediately to patients who have suffered a pulmonary embolus to prevent or to minimize the chances of subsequent pulmonary emboli any one of which may be sufficiently massive to produce death Contrary to an expressed fear extensive experience has demonstrated that there is very little risk that a patient who develops a pulmonary embolus while under anticoagulant therapy will suffer a massive pulmonary hemorrhage The appearance of bloody sputum from an infarcted area constitutes a strong indication for rather than a contraindication to the use of anticoagulants

Both heparin and dicumarol should be administered immediately to patients who have suffered a pulmonary embolus because of the considerable immediate risk of secondary embolism When the patient s prothrombin clotting time has been prolonged satisfactorily heparin may be discontinued and the patient maintained on dicumarol

Priestley Essex and Barker (165) and Murray (166) reported in 1941 series of non fatal pulmonary embolism treated with heparin with gratifying results In Murray s series of 46 cases

TABLE V

INDICATIONS FOR THE USE OF ANTICOAGULANT THERAPY AND SOME CONDITIONS IN WHICH THE USE OF ANTICOAGULANTS HAS BEEN REPORTED FAVORABLY

Indications for Anticoagulant Therapy

1. PULMONARY EMBOLISM DUE TO AN INTRAVASCULAR CLOT to prevent further embolism which may be fatal
2. VENOUS THROMBOSIS (THROMBOPHLEBITIS PHLEBOTHROMBOSIS) to prevent further venous thrombosis and pulmonary embolism and to decrease the chances of chronic venous insufficiency
3. SUDDEN ARTERIAL OCCLUSION DUE TO THROMBOSIS OR EMBOLISM to prevent propagation of a thrombus thrombosis at the site of an embolus or further embolization
4. TRAUMATIC INJURY TO THE BLOOD VESSELS to avoid thrombosis
5. POSTOPERATIVELY AND POSTPARTUM to prevent venous thrombosis and pulmonary embolism in selected cases
6. CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION to prevent thromboembolic complications
7. RHEUMATIC HEART DISEASE WITH AURICULAR FIBRILLATION to prevent embolization
8. GANGRENE OF THE EXTREMITIES to prevent local thrombosis and embolization
9. FROSTBITE
10. GENERAL VASCULAR SURGERY to prevent thrombosis and embolism at operation and postoperatively

Conditions in which the Use of Anticoagulants Has Been Reported Favorably

1. CHRONIC OBLITERATIVE VASCULAR DISEASES when thromboembolic complications have occurred or present a great risk
2. CONGESTIVE HEART FAILURE
3. RETINAL VENOUS OCCLUSION
4. CEREBRAL SINUS THROMBOSIS
5. MESENTERIC THROMBOSIS or EMBOLISM

Conditions in which Anticoagulants Have Been Tried Clinically

1. TOXEMIA OF PREGNANCY
2. MULTIPLE SCLEROSIS

(4) Trauma to the Blood Vessels

Anticoagulant therapy is indicated particularly where there has been a crushing injury to medium sized or large veins Veins of this size particularly if varicosed tend to develop large thrombi which are especially prone to embolization

(5) Chronic Obliterative Vascular Diseases

Anticoagulants have a wide field of application as prophylactic agents They should be administered to patients with chronic obliterative vascular disease whose history includes or suggests a predisposition to thromboembolic phenomena In these patients unless a thromboembolic complication has occurred very recently the patient should be dicumarolized In the presence of a recent thrombosis or embolism heparin should be given immediately

Since there is a considerable permanent risk of thromboembolism in patients with chronic obliterative vascular disease due to the very nature of the primary disease in many instances dicumarol must be administered over long periods of time to minimize the risk of repeated thromboembolic phenomena

(6) Postoperatively and Postpartum

The prophylactic use of anticoagulants following surgical operations or childbirth does not at the present time seem warranted in all instances It is indicated however under the following circumstances

(1) The development of venous thrombosis (thrombophlebitis or phlebothrombosis) and/or pulmonary embolism
(2) History of thromboembolism or of predisposition to thromboembolic phenomena
(3) Extensive pelvic trauma
(4) Certain types of operations which are particularly conducive to thromboembolic complications such as major abdominal and pelvic operations (including major biliary track surgery hysterectomies and gynecological abdomino pelvic surgery intestinal resections and abdomino perineal resections major genito urinary tract surgery *selected* appendectomies hernioplastics major thoracic surgery radical mastectomies and operative procedures on fractures)
(5) Surgical patients over 40 years of age

there was a possible recurrence of pulmonary embolism in 2 patients but the other 44 had no further attacks of embolism and showed a prompt clinical improvement Further experiences with anticoagulant therapy in the treatment of pulmonary embolism are included in the partial review of the literature which follows the section on the postoperative and postpartum use of the anticoagulants

(2) VENOUS THROMBOSIS (THROMBOPHLEBITIS AND PHLEBOTHROMBOSIS)

Anticoagulants should be administered to patients with thrombophlebitis and with phlebothrombosis irrespective of the factors contributing to their development and of the general condition of the patient provided that *none of the contraindications to* be discussed subsequently are present Immediate heparinization is not always necessary in these cases but it is indicated in those patients in whom embolism has already occurred in which the risk of embolization seems great or in which there has been a rapid extension of the thrombophlebitic process The hazard of fatal pulmonary embolism is probably greater when the thrombotic process involves the proximal portion of the femoral canal

In cases of acute thrombophlebitis without embolism or rapid extension and in cases of chronic thrombophlebitis without embolism in which the venous thrombus is probably well attached dicumarol alone will almost invariably suffice

(3) SUDDEN ARTERIAL OCCLUSION

Anticoagulants should be administered to all patients who suffer a sudden arterial occlusion whether it be thrombotic or embolic in origin to prevent the propagation of the initial thrombus and to prevent the detachment of emboli If the occlusion is on an embolic basis heparin and dicumarol should both be administered immediately otherwise dicumarol is usually satisfactory

The importance of anticoagulant therapy in the treatment of sudden arterial occlusion was demonstrated in the early papers of Olovson (167) Groth (168) Murray and Best (55) and Lindgren and Wilander (169) The subject is summarized thoroughly in the text by Allen Barker and Hines (65)

Among conservatively treated cases thrombosis had spread to the thigh in 4 of 5 cases among patients treated with anticoagulants thrombosis had been confined to the lower leg in approximately every second patient When anticoagulant therapy had been ideal thrombosis did not extend above the calf in 4 of 5 cases Patients treated conservatively were in bed on an average of 35 1 days and were febrile for an average of 21 days these periods were reduced to one third or one quarter when anticoagulants were administered Among 214 patients with thrombosis treated conservatively there were 59 cases of pulmonary embolism (28 per cent) 20 of which were fatal among 576 patients treated with anticoagulants there were 8 cases of pulmonary embolism (1 3 per cent) There were three fatal pulmonary emboli one during dicumarol therapy 2 after heparin had been discontinued Thrombosis spread to the opposite leg in 66 patients (30 per cent) treated conservatively but in only 8 patients (1 4 per cent) treated with anticoagulants

When 609 of these patients were traced at the time of reporting it was found that 183 patients who had been treated conservatively for deep venous thrombosis had in most instances both chronic swelling and cyanosis of the lower leg Varicose veins were present in many instances and there were 14 patients with leg ulcers Among 154 patients who had had deep venous thrombosis involving the thigh and who had been treated with heparin there was essentially the same incidence of sequellae after 1 to 5 years as in patients treated conservatively including 11 leg ulcers

However in 130 cases who had had thrombosis in the lower leg only and who had been treated with heparin the majority were symptom free after 1 to 4 years Swelling if it occurred was restricted to the lower leg and was slight often appearing only following straining In all cases there was a striking difference in the condition of those patients whose thrombosis had been confined to the lower leg as compared to those in whom it had progressed to the thigh

Signs of sudden pulmonary embolism without clinical evidence of deep venous thrombosis occurred in 282 cases and in 114 cases led to death so promptly as to preclude specific therapy In 60 autopsies fresh thrombi were observed in the leg veins Of the

(6) Surgery in the presence of intraabdominal and certain other malignancies in which the incidence of thromboembolism is notoriously high

What clinical evidence is there to support these statements? From the myriad of clinical reports which have appeared during the past decade the statistics from a few selected papers are worth reporting

The advantages of treating thrombosis and embolism with heparin was appreciated generally in the Scandinavian countries shortly after the appearance of the early papers by Crafoord (3 12) Bauer (5) and Hellsten (15) It was possible therefore for Zilliacus (16) reporting on 1 158 cases of deep venous thrombosis treated in 20 clinics in Sweden during the years 1940 to 1945 to compare the results obtained by the various forms of therapy by conservative management without anticoagulants and by the use of anticoagulants—heparin heparin and dicumarol or dicumarol alone

Deep venous thrombosis or sudden pulmonary embolism had occurred in 646 (0 51 per cent) of 125 521 surgical patients in 387 (0 4 per cent) of 96 672 obstetric and gynecologic patients and in 125 (0 37 per cent) of 34 086 medical patients The relatively low incidence of thromboembolic complications in this material is explained by the strict selection of cases for analysis and probably also by the widespread use of early mobilization as a prophylactic against thromboembolism

On the basis of the total number of patients admitted the incidence of pulmonary embolism was 0 23 per cent about one third that previously reported For obstetric and gynecologic patients the incidence of pulmonary embolism was 0 09 per cent about one tenth that previously reported

The mortality from pulmonary embolism was 0 1 per cent for surgical patients 0 01 per cent for obstetric and gynecologic patients and 0 053 per cent for medical patients reductions in the various categories of 50 per cent 67 per cent and 83 per cent respectively over figures previously reported

In summary Zilliacus mentions the following features observed in this study

> Among conservatively treated cases thrombosis had spread to the thigh in 4 of 5 cases among patients treated with anti coagulants thrombosis had been confined to the lower leg in approximately every second patient When anticoagulant therapy had been ideal thrombosis did not extend above the calf in 4 of 5 cases Patients treated conservatively were in bed on an average of 35 1 days and were febrile for an average of 21 days these periods were reduced to one third or one quarter when anticoagulants were administered Among 214 patients with thrombosis treated conservatively there were 59 cases of pulmonary embolism (28 per cent) 20 of which were fatal among 576 patients treated with anticoagulants there were 8 cases of pulmonary embolism (1 3 per cent) There were three fatal pulmonary emboli one during dicumarol therapy 2 after heparin had been discontinued Thrombosis spread to the opposite leg in 66 patients (30 per cent) treated conservatively but in only 8 patients (1 4 per cent) treated with anticoagulants

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patients who did not die immediately 65 were treated conservatively and 24 of these died after 24 or more hours the majority after repeated emboli Of 103 cases treated with anticoagulants none died

In a symposium in the *Journal of the American Medical Association* in April 1947 Loewe and Hirsch (170) reported the clinical effect of heparin in Pitkin s menstruum on 168 patients with thrombophlebitis or phlebothrombosis Sixty three of these patients suffered pulmonary embolism and 4 of these died an incidence of fatal pulmonary embolism of 2 4 per cent in the total series and of 6 3 per cent among those in whom pulmonary embolism occurred All four treatment failures occurred before an ideal treatment program was established

Allen Linton and Donaldson (45) presented the experience of the Massachusetts General Hospital with thrombosis and embolism to June 1946 Of 985 patients between the ages of 40 and 64 admitted to a surgical service from January 1 1945 to June 1 1946 162 (16 5 per cent) received 1 or more doses of 200 mg of dicumarol About two thirds of these patients acquired an appreciable elevation of the prothrombin time after a single dose and about one half of the remaining patients reached a satisfactory level after a second dose There were 8 cases of postoperative phlebitis *in this group and 1 instance of sudden death for which the cause* was obscure Of 963 similar patients admitted to another surgical service in the same hospital during the same period and not treated with anticoagulants there were 35 instances of postoperative phlebitis Thus the authors conclude dicumarol given in small doses postoperatively will reduce the incidence of thrombosis and embolism by at least 25 per cent

E V Allen *(164)* reported the experience of the *Mayo Clinic* with dicumarol in 1 686 surgical cases in May 1947 Where possible he utilized for comparison the figures obtained with conservative management at the clinic and reported by Barker Nygaard Walters and Priestly (25) acknowledging that the comparison was not entirely satisfactory In 280 cases of postoperative thrombophlebitis treated with dicumarol there were 7 cases of subsequent *venous thrombosis and 1 cases of minor pul*monary embolism On the basis of the previous experience 68

thromboembolic complications and 16 fatal pulmonary emboli would have been expected Of 716 abdominal hysterectomies treated postoperatively with dicumarol there were 2 instances of minor venous thrombosis and no pulmonary emboli Twenty nine instances of thromboembolism and five fatal pulmonary emboli would have been expected In 292 cases of pulmonary embolism treated with dicumarol there were three cases of subsequent thromboembolism and 1 fatal pulmonary embolus (occurred after the prothrombin time had returned to normal) The anticipated incidence was 127 cases of thromboembolism and 53 instances of fatal pulmonary embolism One hundred and fourteen patients were treated with dicumarol because of a history of previous thromboembolism and 284 patients received dicumarol prophylactically In no instance did venous thrombosis or pulmonary embolism occur

Evans and Dee (171) reported the experience at the Lahey Clinic during the 5 year period 1942 1946 Dicumarol and in the majority of cases heparin also had been used to treat post operative venous thrombosis and pulmonary embolism since April 1941 Among approximately 56 000 major operations performed there were 238 instances of recognized thromboembolic disease (0 42 per cent) Sudden or unrecognized pulmonary embolism occurred in 54 instances In 184 additional cases there were venous thromboses in 123 without embolism and in 61 with a benign pulmonary embolus Sixty three patients received heparin intravenously and 55 received heparin subcutaneously in Pitkin menstruum Three patients received heparin only 63 received dicumarol only Twenty seven patients (15 per cent) were considered refractory to dicumarol and some of these were treated with heparin Venous ligation was performed in 10 of the 184 cases

There were 6 fatalities in these 184 cases One of these was from hemorrhage secondary to dicumarol poisoning and 3 (1 6 per cent of the total) were thromboembolic Of these 3 1 died of a septic embolus and 2 died before adequate anticoagulant therapy had been attained In all 3 instances of fatal thromboembolism a warning embolus had occurred Of interest is the fact that of 61 patients who had suffered a warning pulmonary infarct there were

patients who did not die immediately 65 were treated conservatively and 24 of these died after 24 or more hours the majority after repeated emboli Of 103 cases treated with anticoagulants none died

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Their results are most conveniently presented in tabular form (Table VI)

A recent monograph on venous thrombosis and pulmonary embolism by Neuhof (173) presents a brief review of the literature and a conservative discussion of anticoagulant therapy in these conditions More comprehensive practical discussions of thrombophlebitis and pulmonary embolism including sections on anticoagulant therapy appear in the texts by I S Wright (174) and by Allen Parker and Hines (65)

(7) Coronary Occlusion with Myocardial Infarction

The use of anticoagulants in coronary occlusion with myocardial infarction will be discussed at some length in the following chapter (Chapter 10) Their use in other cardiac conditions will be discussed in the following sections

Subacute Bacterial Endocarditis

It is quite apparent from the literature that the use of heparin or dicumarol as an adjunct to the treatment of subacute bacterial endocarditis with penicillin serves no useful purpose (175 177)

(8) Rheumatic Heart Disease with Auricular Fibrillation

I S Wright (178) first reported that a series of patients who were suffering from rheumatic heart disease and auricular fibrillation and who had experienced multiple emboli prior to the administration of dicumarol were being treated with dicumarol on a long term ambulatory basis The object of administering dicumarol was of course to prevent the further development of mural thrombi and the subsequent detachment of emboli to the pulmonary or systemic circulations

Wright and Foley (179 180) have reported subsequently in considerable detail on the original cases and on additional cases of this nature a total of 19 patients in all who had been kept on dicumarol for periods of from 5 to 20 months (average of 11 months) at the time of reporting The favorable results in these patients kept under dicumarol for periods of months are no less than dramatic and in certain instances patients who were literally invalids prior to the institution of anticoagulant therapy now lead

3 fatal pulmonary emboli and 2 benign pulmonary emboli whereas among the 123 cases of venous thrombosis for which *anticoagulants* had been administered before a pulmonary embolus had occurred there were no pulmonary emboli benign or fatal

The authors conclude that the mortality from postoperative pulmonary embolism was reduced to one fourth in 1945 and to one half in 1946 by the institution of prophylactic exercises by

TABLE VI

SUMMARY OF RESULTS WITH THE ROUTINE USE OF DICUMAROL POSTOPERATIVELY AS A PROPHYLAXIS AGAINST THROMBOEMBOLISM FOLLOWING MAJOR PELVIC AND ABDOMINAL SURGERY WISE LOKER AND BRAMBEL 1948 (172)

	PTS	T E Compl	Emboli	Deaths Pulm Emb	Total Vasc Compl
Controls					
1937–1943	7220	57 (0 8%)	20 (0 3%)	8 (0 1%)	85 (1 0%)
1944–1947	2030	21 (1 0%)	8 (0 4%)	5 (0 2%)	34 (1 6%)
Total	9250	78 (0 8%)	28 (0 3%)	13 (0 14%)	119 (1 2%)
Treated					
1944–1947	5304	4 (0 1%)	1 (0 03%)	*1 (0 03%)	6 (0 18%)

* Probably not due to pulmonary embolism

increased watchfulness for signs of thromboembolism and by the use of anticoagulant therapy with heparin and dicumarol in combination

Wise Loker and Brambel (172) have reported experience with the routine administration of dicumarol postoperatively as a *prophylaxis against thromboembolism following major pelvic* and abdominal surgery at Mercy Hospital in Baltimore In contrast to the more widely accepted usage these authors do not attempt to reduce prothrombin activity below 40 per cent of normal which they consider an adequate maintenance level For controls they utilized 2 groups of patients 2 030 undergoing major abdomino pelvic surgery during the same period of time (1944 1947) but not receiving anticoagulants and 7 220 undergoing similar surgery during the period 1937 1944 and not receiving anticoagulants

300 mg weekly in daily doses of 50 mg six days a week

Following the initial administration of anticoagulants there was an immediate cessation of embolic phenomena and a completely uneventful course She was discharged from the hospital on January 6 1947

She continued to receive anticoagulant therapy while ambulatory She had several episodes of ecchymoses of a very mild degree Her prothrombin time in general was kept between 25 and 35 seconds the highest having been 44 seconds No further embolic episodes occurred in a period of 27 months The patient s general condition was excellent she was able to travel and did so freely and without difficulty whenever satisfactory prothrombin studies could be arranged By planning it was possible for her to travel from New York to the Pacific Coast and return having had prothrombin tests weekly at reliable laboratories en route The trip was without untoward incident Her heart continued in a state of compensated auricular fibrillation

In the spring of 1949 the patient decided to discontinue dicumarol since she had been taking the anticoagulant for two and one half years and had not experienced a thromboembolic episode during that period of time Three weeks after her last dose of dicumarol she suffered a large saddle embolus which lodged at the bifurcation of the aorta Her condition was critical but she recovered slowly on a regime which included both heparin and dicumarol This experience demonstrates the need for *permanent* anticoagulant therapy for patients who have exhibited so profound a tendency to develop thromboembolic complications

L B a 39 year old housewife developed rheumatic fever at 4 years of age From then until she was 12 she had multiple attacks of rheumatic fever and developed a heart lesion In 1941 she developed auricular fibrillation and was found to have mitral stenosis with cardiac decompensation

In February 1946 she had a severe saddle embolus She was then given heparin for 2 weeks The embolus apparently divided descending into both legs and leaving her with occlusion of the major arteries below the knees bilaterally Between February and June 1946 she suffered 6 embolic episodes involving her leg her abdomen and her brain In September 1946 she had an embolus to her right foot and again 1 to each leg

On November 2 1946 she developed a cerebral embolus which produced dizziness diplopia slurring of speech in

completely normal active lives while taking dicumarol regularly

Two of the case reports from the most recent paper by Foley and Wright (180) are republished here with the permission of the authors

E S a 42 year old housewife had typhoid fever at 3 years of age scarlet fever at 4 years and rheumatic fever at 5 years Rheumatic heart disease was recognized during the 6th year Chorea occurred at 6 10 and 12 years of age Since the age of 33 her heart has been in a constant state of auricular fibrillation and during these years she had taken digitalis almost constantly

In 1935 she had an embolus to the left groin and also a pulmonary embolus In 1942 she had a cerebral embolus which produced a right sided hemiplegia from which she made a complete recovery During the years 1943 and 1944 it is estimated that she had at least 6 small emboli to various locations throughout her body In December 1945 she de veloped 2 emboli 1 renal and 1 mesenteric In January 1946 she developed her 13th definite embolus and in September 1946 her 14th embolus both of which were pulmonary

On November 15 1946 she became decompensated and 2 days later there occurred a 15th embolus to the right arm This produced coldness blanching loss of arterial pulsations below the elbow and appeared to endanger the arm On November 19th she developed the 16th embolus to the left leg on November 25th a 17th embolus to the right lung and on December 3rd her 18th to the right lower quadrant of the abdomen producing shock paralytic ileus and later blood in the stool On December 3rd she developed her 19th embolus to the left leg On December 6th she developed a 20th embolus which was to the left forearm and produced marked generalized shock The patient was acutely ill Her outlook appeared extremely serious

On the day of her 20th embolus because of her desperate condition she was started on anticoagulant therapy despite the presence of blood in her stools which was believed due to a mesenteric infarction She received 52 5 mg of heparin intravenously at 9 00 p m December 6th 52 5 mg at 1 00 a m and 50 mg at 6 15 p m December 7th She was also given 300 mg of dicumarol on December 6th followed by daily doses of 200 mg and thereafter was regulated in ac cordance with the indications of her prothrombin clotting times She was continued for 1 month on this regimen while in the hospital Her average requirement of dicumarol was

(10) Toxemia of Pregnancy

Although the pathological changes found at autopsy in women who have died from toxemia of pregnancy are not consistent diffuse capillary or arteriolar lesions occur with considerable regularity in various organs (184) Peripherally located hepatic necrosis observed in some eclamptics may be due to vascular thrombi (184) Sludging of the blood in the conjunctival vessels of eclamptics was reported by Knisely (185) and this observation was confirmed by Odell Aragon and Pottinger (186) For these reasons several observers have considered the possible usefulness of heparin in the treatment of eclampsia and pre eclampsia Preliminary reports have been published by E W Page (187) and by Maeck and Zilliacus (188) In both instances cautious and conservative conclusions while drawn from limited experience have been favorable

(11) Retinal Venous Occlusion

Heparin was first used in the treatment of thrombosis of the central vein of the retina in 1937 by Holmin (189) There have been a number of subsequent reports on the use of heparin in retinal venous occlusion (32 190 192) but though the results are often encouraging the conclusions are cautious There is in fact some disagreement as to the value of anticoagulant therapy (192)

Dicumarol has also been used to a limited extent (193 194) MacLean and Brambel (194) treated 21 cases of vascular retinopathies with dicumarol and rutin and concluded that the results were sufficiently good to warrant further clinical evaluation of dicumarol and rutin in ophthalmology It was their opinion that the absorption of retinal hemorrhages was decidedly more rapid than could have been expected in cases not treated with dicumarol and rutin We have been unable to evaluate this problem in the absence of a large well-controlled series

(12) Cerebral Sinus Thrombosis

Anticoagulants particularly heparin have been used in conjunction with chemotherapy in the treatment of thrombosis of the cavernous and superior longitudinal sinuses (32) but the

> voluntary twitching of the right arm occipital headaches and loss of convergence of the left eye She was admitted to the New York Hospital on November 3rd and dicumarol was started at that time She remained in the hospital for 1 month since which time she has been ambulatory Her average weekly requirement of dicumarol is somewhat higher than that of most patients She needs approximately 800 mg per week to maintain a level between 28 and 35 *seconds She has* had no further emboli and has led a *rather active* life during the past 28 months She has experienced several transient episodes of heart failure

Sprague and Jacobsen (181) have recently reported a case of rheumatic heart disease with periodic arterial embolism who has remained free of thromboembolic complications during the approximately 11 months that he has been under ambulatory treatment with dicumarol

(9) Congestive Heart Failure

Since slowing of the blood stream is one of the principle predisposing causes for thrombosis and since congestive heart failure is the most common cause clinically for a generalized deceleration of the circulation it is not surprising that thromboembolic phenomena are encountered frequently in patients suffering from congestive heart failure (58 71 72 182)

Anderson and Hull (183) have reported a series of 112 patients with congestive heart failure of whom 61 received dicumarol in addition to conventional therapy The incidence of thromboembolic complications in the cases who did not receive dicumarol was 15 per cent the incidence in the group treated with dicumarol was only 8 per cent Furthermore among the 61 treated cases all but 2 of the thromboembolic complications occurred before the institution of anticoagulant therapy In 4 patients who had suffered pulmonary emboli prior to the administration of dicumarol no further thromboembolic episodes occurred after the anticoagulant was given *The mortality in the treated group* was one third lower than that in the group which received no anticoagulant but the difference is not statistically significant

This report can be considered as only preliminary but the results suggest that further studies on the use of anticoagulants in congestive heart failure are justified

(10) Toxemia of Pregnancy

Although the pathological changes found at autopsy in women who have died from toxemia of pregnancy are not consistent diffuse capillary or arteriolar lesions occur with considerable regularity in various organs (184) Peripherally located hepatic necrosis observed in some eclamptics may be due to vascular thrombi (184) Sludging of the blood in the conjunctival vessels of eclamptics was reported by Knisely (185) and this observation was confirmed by Odell Aragon and Pottinger (186) For these reasons several observers have considered the possible usefulness of heparin in the treatment of eclampsia and pre eclampsia Preliminary reports have been published by E W Page (187) and by Maeck and Zilliacus (188) In both instances cautious and conservative conclusions while drawn from limited experience have been favorable

(11) Retinal Venous Occlusion

Heparin was first used in the treatment of thrombosis of the central vein of the retina in 1937 by Holmin (189) There have been a number of subsequent reports on the use of heparin in retinal venous occlusion (32 190 192) but though the results are often encouraging the conclusions are cautious There is in fact some disagreement as to the value of anticoagulant therapy (192)

Dicumarol has also been used to a limited extent (193 194) MacLean and Brambel (194) treated 21 cases of vascular retinopathies with dicumarol and rutin and concluded that the results were sufficiently good to warrant further clinical evaluation of dicumarol and rutin in ophthalmology It was their opinion that the absorption of retinal hemorrhages was decidedly more rapid than could have been expected in cases not treated with dicumarol and rutin We have been unable to evaluate this problem in the absence of a large well-controlled series

(12) Cerebral Sinus Thrombosis

Anticoagulants particularly heparin have been used in conjunction with chemotherapy in the treatment of thrombosis of the cavernous and superior longitudinal sinuses (32) but the

small number of cases reported and the relatively good results obtained by the use of sulphonamides and more recently the antibiotics alone makes it difficult to evaluate the role of heparin or dicumarol It is perhaps significant that the majority of cases reported in which anticoagulants have been used have recovered rather promptly and with a minimum of residual sequellae The data however are inadequate to warrant any conclusions at present

(13) Frostbite and Gangrene of the Extremities

A considerable number of reports have appeared suggesting that anticoagulants are indicated in the treatment of gangrene of the extremities whether post traumatic arteriosclerotic diabetic or secondary to frostbite (32 52 195 197) Lange and Loewe (52 195 196) have convincingly demonstrated the beneficial effects of heparin in acute frostbite induced experimentally in animals and man They have also acquired a somewhat limited experience with clinical material

Brambel and Loker (197) reported a series of 11 cases of gangrene in 6 following crush injuries in 3 complicating diabetes and in 1 complicating frostbite Although amputation seemed inevitable in all instances treatment with dicumarol was accompanied by such improvement that amputation was often avoided The authors believe that anticoagulant therapy in patients with arteriosclerotic and diabetic gangrene of the toes may permit amputation at a site of election below the knee rather than the mid thigh amputations which are so commonly done Further work is necessary to evaluate fully these claims

(14) Mesenteric Thrombosis and Embolism

The use of anticoagulants in mesenteric thrombosis is of particular interest because of the discouragingly high mortality rates reported ordinarily The clinical experience of Murray and MacKensie (34 198) has been supported by many isolated case reports (32) and indicates that heparin is of extraordinary value in the treatment of mesenteric venous thrombosis in its earlier stages

However Laufman (199 200) has shown experimentally in dogs and his findings have been confirmed clinically that the chances of recovery when segments of the intestine have been deprived of their blood supply either by occlusion of the mesenteric vessels or by strangulation is very small unless resection is performed Heparin may facilitate a fatal outcome by promoting the escape of blood and fluid into the peritoneal cavity and into the bowel Since this may occur even after resection the post operative administration of heparin must be carried out with the utmost caution

When the mesenteric occlusion is embolic anticoagulant therapy would appear to be indicated to prevent further emboliza tion from the original source

(15) General Vascular Surgery

The use of heparin in general vascular surgery particularly in connection with embolectomy has been treated in detail by Murray and his coworkers (31 55 166 201 204) and is well summarized by Jorpes (32)

(16) Multiple Sclerosis

There is considerable evidence that multiple sclerosis and certain encephalomyelitides are related in some way to vascular damage within the central nervous system most probably the result of thrombosis of the venules (49) Putnam and his associ ates were led to believe that local lesions might be prevented by decreasing the coagulability of the blood as had been the case with experimental encephalomyelitis produced by the intravenous in jection of certain coagulants As early as 1924 Putnam and Hoefer reported that cysteine is a feeble anticoagulant which tends to prevent relapses in cases of multiple sclerosis (205) In May 1944 Reese (206) reported that he had treated 28 cases of multiple sclerosis for periods up to 6 months with dicumarol but his results were disappointing Although all patients experienced subjective improvement objective improvement was not noted

In January 1947 Putnam et al (49) reported that they had ad ministered dicumarol to 43 patients with multiple sclerosis for periods of from 6 months to 4 years Dicumarol was administered

small number of cases reported and the relatively good results obtained by the use of sulphonamides and more recently, the antibiotics alone makes it difficult to evaluate the role of heparin or dicumarol It is perhaps significant that the majority of cases reported in which anticoagulants have been used have recovered rather promptly and with a minimum of residual sequellae The data however are inadequate to warrant any conclusions at present

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Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction

THE possibility of utilizing anticoagulants to prevent the extension of coronary thrombi and the development of mural thrombi in the presence of myocardial infarction was suggested by Solandt, Nassim and Best (142, 143) in 1938. Their observations were not applied to man on any significant scale because of the difficulties, risk and expense inherent in the use of heparin clinically at that time.

Prior to 1945 there were sporadic accounts of individual cases of coronary occlusion with myocardial infarction being treated with dicumarol (208), but the first definitive papers on this type of treatment were those by I. S. Wright (209, 210), by Nichol and Page (208) and by Peters, Guyther and Brambel (211). Wright (178, 179, 212-214), Nichol and Fassett (215, 216) and Peters, Doenges and Brambel (217) have supplemented their original reports as their experience has increased. Other original observations have been reported by Cotlove and Vorzimer (218), Parker and Barker (219, 220), Glueck and her associates (221), McCall (222), Reich and Eisenmenger (223), Greismen and Marcus (224) and others.

The uniformly favorable results, although in no instance of sufficient magnitude nor sufficiently well controlled to warrant statistical treatment, justified a more extensive study and led directly to the formation of the *Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction* by the American Heart Association in the spring of 1946.

THE AMERICAN HEART ASSOCIATION STUDY[1]

The committee and the sixteen hospitals which have con-

[1] The remainder of this chapter is a condensation of the preliminary report of the Committee which appears in full in the *Journal of the American Med*

(Continued on page 82)

in amounts sufficient to prolong the prothrombin time to 30 seconds Twenty five patients suffering from a remittant form of the disease were adequately treated without interruption for a total period of 61 patient years In this group no fresh symptoms or obvious acute outbreaks occurred The majority of 16 patients with chronic progressive multiple sclerosis continued on their downhill course Two patients who remained free of new symptoms while on dicumarol suffered acute relapses when anticoagulant therapy was interrupted In 2 patients in whom large doses of dicumarol failed to produce the expected increase in prothrobin time relapses occurred

Olwin (207) has commented on his experience with four patients with multiple sclerosis who were treated with dicumarol One patient a woman of 22 has shown continued improvement over a period of about 8 months the other 3 women over the age of 30 have shown no objective improvement during therapy

Certainly further evidence that anticoagulants are of value in multiple sclerosis must be presented before they can be recommended generally for this disease

Plan of the Study

Slightly fewer than one half of these one thousand cases were treated by conventional methods of therapy alone The others received anticoagulants in addition to conventional therapy A detailed record of each case was forwarded on master forms by the responsible investigator and his associates to the Central Office of the committee at the New York Hospital where they are being subjected to intensive statistical analysis A definitive report on the 1 031 cases will be prepared as promptly as the analysis permits

The data reported here have been obtained from a limited analysis of the first 800 cases (225 226) Although the addition of the last 200 cases and other later revisions may change the figures somewhat it is unlikely that the conclusions will be altered significantly since the relationship of deaths and thromboembolic complications in the control and treated groups remained relatively stable as the sample grew

The principles to be used as guides in the administration of dicumarol and heparin were outlined at the beginning of the study as follows

a Heparin may be given for the first 48 hours or more if desired
b Prothrombin determinations are to be done each day and no dicumarol should ever be ordered unless the morning prothrombin report is available
c Dicumarol 200 300 mg daily should be given until the prothrombin time reaches 30 seconds
d Dicumarol 50 to 100 mg daily should be given if the prothrombin time is between 30 and 35 seconds
e Dicumarol is withheld if the prothrombin time is 35 seconds or more Then no drug is given until the prothrombin time is again down to 30 seconds or less after which the drug is again given cautiously in 100 mg doses
f The Link Shapiro technique using undiluted whole plasma or the Quick method is to be used for determining the prothrombin clotting time It is suggested that the Link Shapiro method using 12 5 per cent diluted plasma be employed as an additional safeguard All prothrombin times are given in terms of the Link Shapiro (undiluted) method
g Unless contraindications arise the dicumarol therapy is to

TABLE VII

THE PARTICIPATING HOSPITALS AND RESPONSIBLE INVESTIGATORS *COMMITTEE FOR EVALUATION OF ANTICOAGULANTS IN THE TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION* AMERICAN HEART ASSOCIATION

Participating Hospitals	*Responsible Investigators*
Bellevue Hospital New York	John E Deitrick M D
Beth Israel Hospital Boston	Herrman L Blumgart M D
Bronx Veterans Hospital New York	Louis A Kapp M D
Cincinnati General Hospital	Johnson McGuire M D
	Helen Glueck M D
Cleveland City Hospital	Roy W Scott M D
Henry Ford Hospital Detroit	F Janney Smith M D
Jackson Memorial Hospital Miami	E Sterling Nichol M D
Lakeside Hospital Cleveland	Joseph Hayman Jr M D
	Harold Feil M D
Massachusetts General Hospital Boston	Howard B Sprague M D
Michael Reese Hospital Chicago	Louis N Katz M D
Mount Zion Hospital San Francisco	John J Sampson M D
Pennsylvania Hospital Philadelphia	Joseph M Vander Veer M D
Peter Bent Brigham Hospital Boston	Samuel A Levine M D
Rhode Island Hospital Providence	Frank B Cutts M D
San Francisco County Hospital	John J Sampson M D
The New York Hospital	Irving S Wright M D
	Harold J Stewart M D

Consultants

Ralph S Overman Ph D	Nelson W Parker M D
Charles E Brambel Ph D	Grace Goldsmith M D

Central Laboratory

Irving S Wright M D Chairman of Study
Charles D Marple M D Coordinator
Dorothy F Beck Ph D Statistician

tributed cases to this study are listed in Table VII Additional workers in these and other institutions have participated in an advisory or consulting capacity Over 1 000 cases of coronary occlusion with myocardial infarction have been studied under the conditions of this investigation

ical Association 138 1074 1079 December 11 1948 and in the *American Heart Journal* 36 801 815 December 1948

whom anticoagulants were withheld because of specific contra indications since these are considered to be disadvantages inherent to this type of therapy In both groups all rates for thromboembolic complications and hemorrhagic manifestations refer to conditions diagnosed clinically Statistics on autopsy findings are not yet available

TABLE VIII

COMPOSITION OF SAMPLE*

Item Compared	Control Group (Even Days)	Treated Group (Odd Days)
Number of cases	368	432
Average age	60 years	59 years
Proportion males	77%	76%
One or more previous infarctions	24%	22%
Illness severe at onset	23%	30%
Anticoagulant therapy received (exceptions as noted)	88% no anticoagulants 12% some anticoagulants (primarily after complications)	81% dicumarol without heparin 12% dicumarol plus some heparin 3% no anticoagulants because of renal or liver disease or hemorrhage 2% no anticoagulants because of miscellaneous errors

* Total group 800 patients with coronary occlusion with myocardial infarction surviving the first day of hospitalization

A comparison of the patients in the control group with those in the treated group shows a striking similarity in regards to age history of previous infarction and estimated severity of the previous attack as shown in Table VIII The average age of the control group was 60 years that of the treated group 59 years The average age of the control group of males was 58 9 years that of the treated group 57 2 years The average age of the control group of females was 64 1 years that of the treated group 64 6 years In this series of 800 patients the average for females was approximately 6 4 years older than that for males Twenty four per cent

be continued in the chosen cases over a minimum period of 30 days preferably 30 days after the last thromboembolic episode

h In instances of hemorrhagic manifestations the use of synthetic Vitamin K preparations in doses of 60 75 mg and transfusions of fresh whole blood (may be citrated) are recommended [2]

Of the first 800 patients 368 admitted to the participating services on *even* days received conventional therapy only and constitute the control group Four hundred and thirty two patients admitted on *odd* days received anticoagulants in addition to conventional therapy and constitute the treated group

Eighty eight per cent of patients in the control group received *no anticoagulant* but 12 per cent did receive some anticoagulant therapy often for short periods only Anticoagulants were administered to patients in the control group following the development of a thromboembolic complication because of the insistence of the patient s family or his private physician or for miscellaneous reasons *Of the treated group 81 per cent received dicumarol* only while 14 per cent received dicumarol and some heparin In three per cent of the treated cases no anticoagulants were given because of concurrent renal or hepatic disease or because of hemorrhagic conditions and 2 per cent received no anticoagulant because of miscellaneous errors

In the computation of the rates upon which all of the following charts are based small and conservative corrections were made in *order to simplify the presentation* [3] *In the control group the rates* were corrected for exceptions to the no anticoagulant rule Rates as shown are those it is estimated would have occurred if no case in the control group had received any anticoagulant They differ only slightly from the data as actually reported and are believed to present a truer picture of rates without anticoagulants With more intensive anticoagulant therapy the rates for deaths and complications in the treated group would have been lower than those shown *No correction was made for those patients from*

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[2] From the instructions issued to each participating team—slightly modified

[3] The corrections for exceptions proved to be small and sometimes were completely without effect on the rates They do not alter at any point the basic differences between groups from which conclusions are drawn

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of the control group and 22 per cent of the treated group had experienced one or more previous infarctions

An estimate of the severity of the attack was made for each patient at the time of diagnosis Twenty three per cent of the control group and 30 per cent of the treated group were classified

cases dying in control and treated groups under study

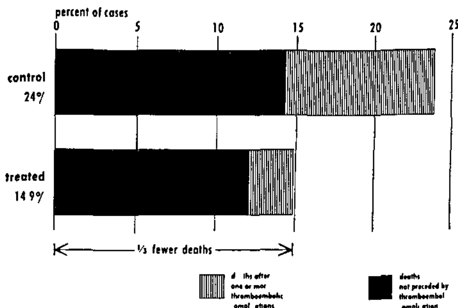


FIGURE 5 Percentage of deaths in the control and treated groups studied indicated by the horizontal row of figures at the top The upper bar shows *results in the control group (24 per cent) and the lower bar in the treated* group (14 9 per cent) one third fewer deaths than in the control group The hatched areas indicate deaths after one or more thromboembolic complications and the darkened areas indicate deaths not preceded by a thromboembolic complication

as having severe attacks Although this classification is arbitrary the results suggest that the treated group contains a somewhat greater proportion of severely ill patients The control and treated groups were closely similar when the medical histories of cardiovascular diseases and the location of their original infarcts were compared

Results of the Study

Deaths (Figure 6) Twenty four per cent of the control patients died whereas 15 per cent of the treated patients died Thus somewhat more than one third of the individuals who would have died without anticoagulant therapy survived the specific attack under consideration when anticoagulants were given This differ

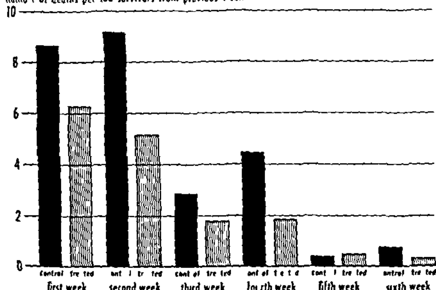


FIGURE 6 Death rates by week of illness The number of deaths per hundred survivors from the previous week is shown in the vertical column of figures on the left

ence is statistically significant [*] Further examination indicates that the greatest improvement was achieved in patients who had suffered one or more thromboembolic complications prior to

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The term statistically significant is used throughout the text to mean that the chances that two random samples from the same population would yield on the basis of chance alone differences as great as those observed and in the same direction are less than one in one hundred In most instances the chances of obtaining these differences in 2 samples from the same universe are in fact much less—in the case of thromboembolic complications less than one in a thousand

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An estimate of the severity of the attack was made for each patient at the time of diagnosis Twenty three per cent of the control group and 30 per cent of the treated group were classified

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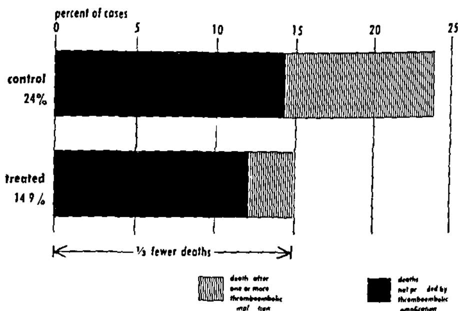


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as having severe attacks Although this classification is arbitrary the results suggest that the treated group contains a somewhat greater proportion of severely ill patients The control and treated groups were closely similar when the medical histories of cardiovascular diseases and the location of their original infarcts were compared

coagulant treatment should be continued for at least 4 weeks after the last thromboembolic episode

The greatest benefits in the reduction of mortality are in patients 60 years or older (Figure 7) Hemorrhagic complications have been so few and so mild throughout the entire study and the benefits of treatment in the older age group so pronounced that we do not hesitate to prescribe anticoagulants to older patients It should be recognized that older patients have a higher incidence of unrelated complications and that careful consideration of such factors is mandatory While the crude death rates for patients

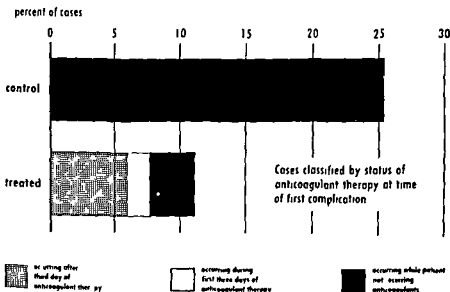


FIGURE 8 Percentage of cases in which one or more thromboembolic complications developed and the time when the complications occurred Cases were classified by the status of anticoagulant therapy at the time of the first complication The upper bar is of the control group and the lower bar of the treated group The horizontal row of figures at the top indicates the percentage The checked area indicates complications occurring after the third day of anticoagulant therapy the blank area indicates complications occurring during the first three days of anticoagulant therapy and the darkened areas indicate complications occurring while the patient was not receiving anticoagulants

death Such deaths occurred in roughly 10 per cent of the control cases but in only 3 per cent of the treated cases Death not preceded by a clinically recognized thromboembolic complication occurred in approximately 14 per cent of the controls as against 12 per cent in the treated group As previously anticipated anticoagulant reduced the death rate largely by reducing the number of deaths due directly or indirectly to thromboembolism

The death rates by week of illness (Figure 6) were highest during the first 2 weeks but were still considerable during the 3rd and 4th weeks For each period the death rate for the control patients was found to be significantly greater than that for the treated group These figures indicate that anticoagulant therapy if not used before should be begun as late as the 2nd or 3rd weeks after a myocardial infarction has occurred—or later if complications have developed and that to give maximal protection anti

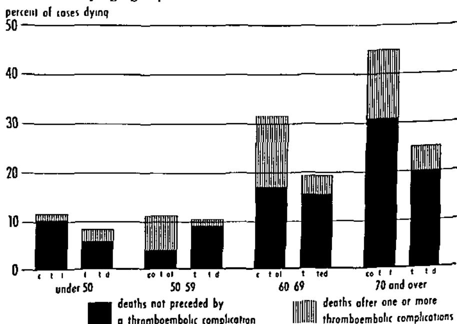


FIGURE 7 Death rates by age groups The percentage of patients who died is shown in the vertical column of figures The darkened areas indicate deaths not preceded by a thromboembolic complication and the hatched areas indicate deaths after one or more thromboembolic complications

ence is statistically significant However of these treated cases 3 5 per cent developed their first complication before they had received any anticoagulant[5] and 1 5 per cent developed their first thromboembolic complication during the first 3 days of anti coagulant therapy before dicumarol is ordinarily fully effective Thus 5 per cent developed thromboembolic complications when anticoagulant therapy could not have been fully effective Only 6 per cent of the patients developed thromboembolic complica tions while they were actually under the full effect of anticoagu lant therapy

The number of thromboembolic complications diagnosed clin ically per hundred cases was 36 in the control group and only 14 in the treated group (Figure 9) In other words the patients in the treated group experienced slightly more than one third as many thromboembolic complications as did the control group a contrast which is highly significant statistically

This contrast is further emphasized by the facts that 5 throm boembolic complications per 100 cases developed in the treated group while the patients were not receiving anticoagulant therapy and 2 5 complications per 100 cases developed during the first 3 days of anticoagulant therapy Actually then only 6 5 thromboembolic complications per 100 treated cases occurred in patients who were under the full therapeutic effect of anticoagu lant therapy This figure includes complications in some patients whom we would not now consider to have been under adequate therapy at the time the complication occurred

Autopsies were conducted on 18 per cent of the patients who died among the total series of 800 and will be reported in detail in the definitive report of this study

The highest incidence of thromboembolic complications among the control patients occurred in the age group between 50 and 59 years in distinct contrast to the death rate by age groups (Figure 10) The explanation for this contrast appears to be that while the younger patients suffer numerous thromboembolic complica tions and while some of these complications result in permanent damage the younger patients are able to survive them Thus an

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Included in this group are those who never received anticoagulants because of contraindications

number of thromboembolic complications

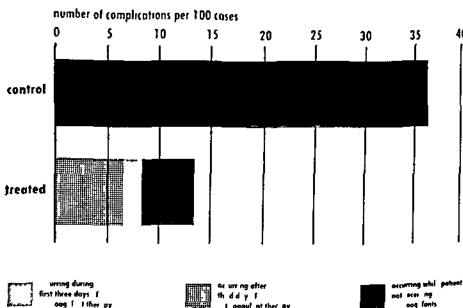


FIGURE 9 Number of thromboembolic complications The upper bar is of the control group and the lower bar of the treated group The horizontal row of figures at the top indicates the number of complications per hundred cases The dotted area indicates the complications occurring during the first three days of anticoagulant therapy the checked areas indicate complications occurring after the third day of anticoagulant therapy and the darkened areas indicate complications occurring while the patient was not receiving anticoagulants

under 59 in the treated and control groups did not show a significant difference the incidence of thromboembolic complications is high in these age groups and the treated cases show a much lower incidence of thromboembolic complications Such thromboembolic complications may not only be serious incidents in themselves but they may result in such serious permanent disabilities as hemiplegia (following cerebral embolism) chronic venous insufficiency (following thrombophlebitis) or residual myocardial damage (following repeated myocardial infarction)

Thromboembolic Complications Twenty five per cent of the control cases and only 11 per cent of the treated cases developed at least one thromboembolic complication (Figure 8) This differ

throughout the first 4 weeks This demonstrates the importance of beginning anticoagulant therapy even as late as the 2nd or 3rd week following a myocardial infarction *Since it is impossible to predict from the condition of the patient during the first week whether he will develop thromboembolic complications during subsequent weeks and whether he will die from them it is import-*

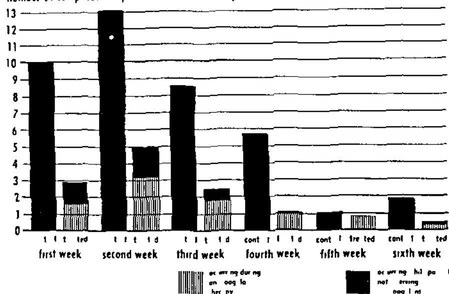


FIGURE 11 Number of thromboembolic complications by week of illness *The vertical column of figures* shows the number of complications per hundred survivors from the previous week The hatched areas indicate the complications occurring during anticoagulant therapy and the darkened areas indicate the complications occurring while the patient was not receiving anticoagulants

ant to give anticoagulant therapy to all patients with coronary occlusion and myocardial infarction unless specific contraindications exist

The types and locations of thromboembolic complications and the effects of anticoagulant therapy in each group have been determined (Figure 12) There was evidence of extension of the original myocardial infarct in 9 cases per hundred in the controls

individual under 60 may have repeated thromboembolic complications without a fatal episode whereas an older patient may succumb to the initial attack and hence not have an opportunity of developing repeated thromboembolic attacks This indicates clearly the importance of preventing the thromboembolic complications in all age groups Within the treated group when a dis

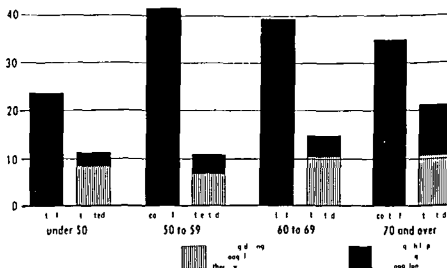


FIGURE 10 Number of thromboembolic complications by age groups The hatched areas indicate the complications occurring during anticoagulant therapy and the darkened areas indicate the complications occurring while the patient was not receiving anticoagulants

tinction is made between those actually receiving anticoagulants and those who were not receiving anticoagulants at the time of their thromboembolic complications the effects of anticoagulant therapy are further emphasized

When the rate of thromboembolic complications by week of illness is considered (Figure 11) the advantage of using anticoagulants is clearly demonstrated for each of the first 4 weeks of the illness As is the case with deaths the incidence of thromboembolic complications highest in the 2nd week is marked

throughout the first 4 weeks This demonstrates the importance of beginning anticoagulant therapy even as late as the 2nd or 3rd week following a myocardial infarction *Since it is impossible to predict from the condition of the patient during the first week whether he will develop thromboembolic complications during subsequent weeks and whether he will die from them it is import*

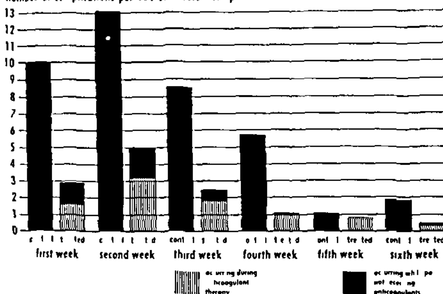


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The types and locations of thromboembolic complications and the effects of anticoagulant therapy in each group have been determined (Figure 12) There was evidence of extension of the original myocardial infarct in 9 cases per hundred in the controls

individual under 60 may have repeated thromboembolic complications without a fatal episode whereas an older patient may succumb to the initial attack and hence not have an opportunity of developing repeated thromboembolic attacks This indicates clearly the importance of preventing the thromboembolic complications in all age groups Within the treated group when a dis-

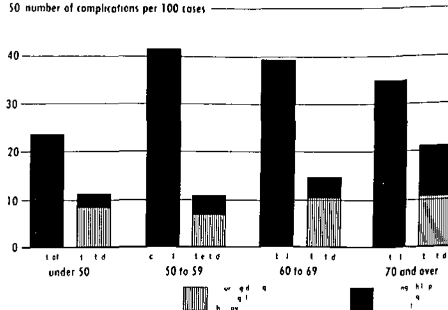


FIGURE 10 Number of thromboembolic complications by age groups The hatched areas indicate the complications occurring during anticoagulant therapy and the darkened areas indicate the complications occurring while the patient was not receiving anticoagulants

tinction is made between those actually receiving anticoagulants and those who were not receiving anticoagulants at the time of their thromboembolic complications the effects of anticoagulant therapy are further emphasized

When the rate of thromboembolic complications by week of illness is considered (Figure 11) the advantage of using anticoagulants is clearly demonstrated for each of the first 4 weeks of the illness As is the case with deaths the incidence of thromboembolic complications highest in the 2nd week is marked

boembolic complications than did those who received the conventional form of therapy alone.

Hemorrhagic Complications. Hemorrhagic complications numbered 6 per hundred in the control group and slightly more than 12 per hundred among the treated cases (Figure 13). It should be noted, however, that of these complications in the latter

relation of hemorrhagic manifestations to anticoagulants

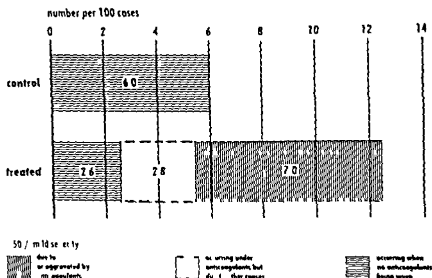


FIGURE 13. Relation of hemorrhagic manifestations to anticoagulants. The upper bar is of the control group and the lower bar of the treated group. The hemorrhagic manifestations were mild in 50 per cent of the cases. The horizontal line of figures at the top shows the number of hemorrhagic manifestations per hundred cases. The area with vertical hatching indicates that the hemorrhagic manifestations were due to or aggravated by anticoagulant therapy; the blank area indicates occurrence while the patient was receiving anticoagulants but due to other causes; and the areas with horizontal hatching show occurrence when no anticoagulants were being given.

group, 2 in 12 developed in patients who were not under anticoagulant therapy when their hemorrhage occurred. In an additional 3 the hemorrhages were known to be due to causes other than anticoagulants and not to be aggravated by that therapy. The total hemorrhagic manifestations in the treated group

as against 2 cases per hundred in those treated There was infarction of new areas in the myocardium in 6 5 cases per hundred in the controls as against 2 5 among those treated Pulmonary emboli occurred in 9 4 cases per hundred among the controls as against 5 2 cases among the treated and half of the latter were not actually receiving anticoagulant therapy at the time they suffered

types and locations of thromboembolic complications

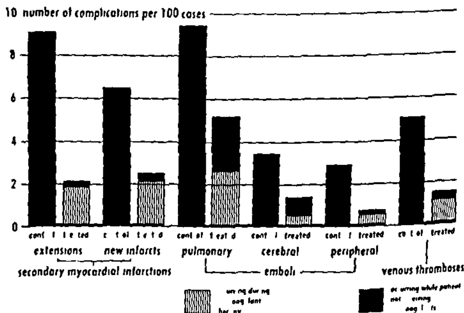


FIGURE 12 Types and locations of thromboembolic complications The hatched areas indicate the complications occurring during anticoagulant therapy and the darkened areas indicate the complications occurring while the patient was not receiving anticoagulants

their pulmonary embolism Cerebral emboli occurred in 3 4 per hundred of the control cases as against 1 4 per hundred among the treated cases Peripheral emboli developed in 3 per hundred of the control cases as against 1 per hundred of the treated and venous thrombosis occurred in 5 per hundred of the control cases and in less than 2 per hundred of the treated

It is evident that at every site and with every type of complication those receiving anticoagulant treatment in addition to conventional therapy had a distinctly better chance of escaping throm

boembolic complications than did those who received the conventional form of therapy alone

Hemorrhagic Complications Hemorrhagic complications numbered 6 per hundred in the control group and slightly more than 12 per hundred among the treated cases (Figure 13) It should be noted however that of these complications in the latter

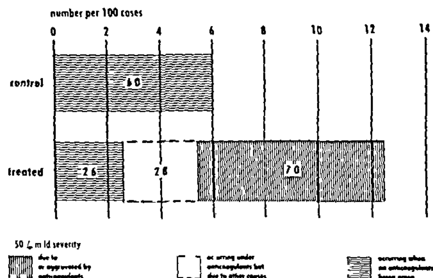


FIGURE 13 Relation of hemorrhagic manifestations to anticoagulants The upper bar is of the control group and the lower bar of the treated group The hemorrhagic manifestations were mild in 50 per cent of the cases The horizontal line of figures at the top shows the number of hemorrhagic manifestations per hundred cases The area with vertical hatching indicates that the hemorrhagic manifestations were due to or aggravated by anticoagulant therapy the blank area indicates occurrence while the patient was receiving anticoagulants but due to other causes and the areas with horizontal hatching show occurrence when no anticoagulants were being given

group 2 in 12 developed in patients who were not under anticoagulant therapy when their hemorrhage occurred In an additional 3 the hemorrhages were known to be due to causes other than anticoagulants and not to be aggravated by that therapy The total hemorrhagic manifestations in the treated group

which are known to be due to causes other than anticoagulants approaches that found in the control group An additional 7 per hundred cases however were believed to be due to or aggravated by anticoagulants The incidence of severe hemorrhage resulting from anticoagulant therapy was extremely low Of the 30 hemorrhages clinically observed 15 (50 per cent)

sources of bleeding in hemorrhagic manifestations

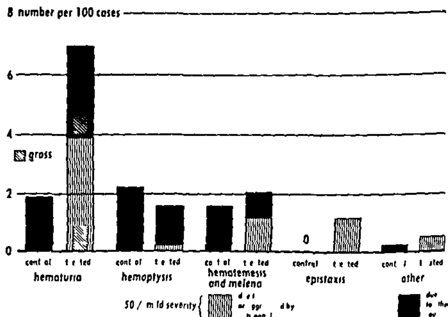


FIGURE 14 Sources of bleeding in hemorrhagic manifestations Fifty per cent of the manifestations were mild The areas of diagonal hatching indicate gross hemorrhage the areas of vertical hatching indicate hemorrhagic manifestations due to or aggravated by anticoagulant therapy and the darkened areas indicate hemorrhagic manifestations due to other causes

were mild in severity 14 (47 per cent) were moderately severe and only 1 (3 per cent) was severe

The autopsies examined to date present no alarming picture of hemorrhagic risks in anticoagulant therapy under proper controls As discussed in Chapter 8 Blumgart and his coworkers (160 161) Beattie et al (162) and LeRoy and Nalefsky (163) working with dogs whose coronary arteries had been ligated

found that dicumarolized animals showed no increase of hemorrhage in the myocardium endocardium or pericardium as compared with non dicumarolized animals

When the sources of bleeding are considered (Figure 14) it is evident that there is a definite incidence of hemorrhage in the control group in each of the categories except that of epistaxis Hemorrhages due to causes other than anticoagulants also occur in 3 of the categories in the treated group It will be noted that hemorrhages occurred more frequently in the treated group in all categories except for that of hemoptysis which occurred more frequently in the control cases The explanation for the greater incidence of hemoptysis in the control patients is that pulmonary infarction is much more common in these patients than among the treated cases

Intimal Hemorrhage and Coronary Occlusion

Paterson (227 229) and Wartman (230) have suggested that hemorrhage into the intima of a coronary artery from intimal sinusoidal vessels is an important precipitating factor in the production of coronary thrombosis Similar processes have been described by Paterson in atherosclerotic cerebral (231) and pulmonary vessels (232) Intimal hemorrhage in the coronary vessels had previously been interpreted as part of an exudative inflammatory reaction by Boyd (233) and as a result of regurgitation from the lumen into the intima following rupture of an atheromatous abscess by Leary (234)

The view that intramural hemorrhage is the primary process in many instances of coronary obstruction and that it may frequently lead to intraluminal thrombosis has been supported by Winternitz et al (235) Horn and Finkelstein (236) and Nelson (237) English and Willius (238) on the other hand concluded that The intimal changes that coexisted with the hemorrhage appeared to represent the primary factor in the pathologic condition the hemorrhage was secondary It does not seem logical moreover that hemorrhage in itself can have produced the effects observed

That intimal hemorrhages occur commonly in atherosclerotic coronary arteries and often in association with coronary occlusion

which are known to be due to causes other than anticoagulants approaches that found in the control group. An additional 7 per hundred cases, however, were believed to be due to or aggravated by anticoagulants. The incidence of severe hemorrhage resulting from anticoagulant therapy was extremely low. Of the 30 hemorrhages clinically observed, 15 (50 per cent)

sources of bleeding in hemorrhagic manifestations

8 number per 100 cases

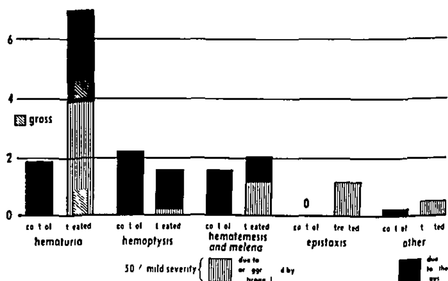


FIGURE 14. Sources of bleeding in hemorrhagic manifestations. Fifty per cent of the manifestations were mild. The areas of diagonal hatching indicate gross hemorrhage; the areas of vertical hatching indicate hemorrhagic manifestations due to or aggravated by anticoagulant therapy; and the darkened areas indicate hemorrhagic manifestations due to other causes.

were mild in severity, 14 (47 per cent) were moderately severe, and only 1 (3 per cent) was severe.

The autopsies examined to date present no alarming picture of hemorrhagic risks in anticoagulant therapy under proper controls. As discussed in Chapter 8, Blumgart and his coworkers (160, 161), Beattie et al. (162), and LeRoy and Nalefsky (163), working with dogs whose coronary arteries had been ligated

CHAPTER 11

Contraindications to the Use of the Anticoagulants

THERE are a limited number of circumstances in which the anticoagulants are to be used cautiously or not at all These are listed in Table IX and are discussed briefly for the most part in the following sections

(1) HYPOPROTHROMBINEMIA (239 241)

Prothrombin is believed to be produced solely by the liver and vitamin K is necessary for its synthesis It is not known whether vitamin K enters into the prothrombin molecule itself or whether it acts as a component of an enzyme system concerned with the formation of prothrombin A deficiency of vitamin K leads to a deficiency of prothrombin in the blood and except in those instances when there is severe liver damage prothrombin deficiency secondary to the lack of vitamin K can be corrected by the administration of the vitamin

Vitamin K is provided in the normal diet and it is synthesized by bacteria in the gastrointestinal tract Since it is a fat soluble vitamin bile must be present in the intestine before vitamin K can be absorbed The only known effect of vitamin K deficiency is hypoprothrombinemia and the only recognized manifestation of the deficiency the bleeding tendency which results from hypo prothrombinemia The coagulation time of the whole blood is ordinarily not prolonged unless the prothrombin concentration is very low the bleeding time is normal

Since the liver is the site of prothrombin formation severe intrinsic disease of the liver and other conditions which impair its function may produce hypoprothrombinemia When hypo prothrombinemia results entirely from decreased synthesis of prothrombin due to impaired hepatic function the administra tion of vitamin K will not increase the plasma prothrombin

has been demonstrated repeatedly when serial sections of these arteries have been studied at autopsy Such studies show that occasionally the intimal hemorrhage is sufficiently extensive to produce an intermural hematoma which in itself can block the coronary vessel A lesser hemorrhage may still produce partial obstruction of and stasis in the coronary vessel or endothelial damage Necrosis of the endothelium may permit the hemorrhage to rupture into the lumen of the coronary vessel It is not clear from these studies that such intimal hemorrhages are frequently the immediate cause for coronary thrombosis

The favorable results obtained with anticoagulant therapy in many hands indicate that it probably does not ordinarily aggravate existing subintimal hemorrhage In instances where an intimal hemorrhage produces endothelial damage or ruptures into the lumen of a coronary artery anticoagulant therapy interferes with the development of intraluminal thrombosis

TABLE X

CLINICAL CONDITIONS WHICH MAY PRODUCE HYPOPROTHROMBINEMIA

1 *Deficient Availability of Vitamin K*
  a Inadequate intake (simple dietary deficiency)
    i Malnutrition
    ii Pan avitaminosis
    iii Vitamin K deficient diets—low fat diets
    iv Anorexia nervosa
  b *Interference with synthesis in the intestine*
    i Administration of certain sulfonamides
    ii Hemorrhagic disease of the newborn (?)
    iii Intrinsic diseases of intestine
2 Deficient Absorption of Vitamin K
  a Absence of bile salts from the intestine
    i Obstructive jaundice
    ii External biliary fistula
  b Interference with digestion of fats
    i Pancreatic disease
    ii Idiopathic Steatorrhea
    iii Celiac disease
  c Accelerated or interrupted flow of intestinal content
    i Chronic vomiting or diarrhea
    ii Gastrointestinal intubation
    iii Gastrointestinal anastomoses resections and fistulae
  d Loss of normal absorbing surface
    i Ulcerative colitis regional ileitis etc
    ii Short circuiting operations and resections
3 Deficient Synthesis of Prothrombin (deficient utilization of Vitamin K)
  a Diseases of the liver (hepatocellular damage)
    i Cirrhosis of the liver
    ii Primary or metastatic malignancy
    iii Acute hepatitis and infectious hepatitis (catarrhal jaundice)
    iv Acute yellow atrophy
  b Experimental
    i Hepatic poisons (chloroform carbon tetrachloride etc)
    ii Partial or complete hepatectomy
4 Miscellaneous causes for Hypoprothrombinemia
  a Idiopathic Hypoprothrombinemia
  b Hypoprothrombinemia of the newborn (hemorrhagic disease of the newborn)
  c Traumatic and hemorrhagic shock
  d The effect of certain drugs
    i Salicylates ii Sulphonamides iii Dicumarol

activity However in many instances of moderately impaired liver function hypoprothrombinemia results from the combined effect of vitamin K deficiency due to poor absorption and depressed prothrombin synthesis due to the liver damage In such instances the prothrombin activity of the plasma may be partly restored by the administration of vitamin K parenterally

TABLE IX

CONDITIONS IN WHICH ANTICOAGULANTS MUST BE USED CAUTIOUSLY OR NOT AT ALL

1 PROTHROMBIN DEFICIENCY (HYPOPROTHROMBINEMIA) or potential prothrombin deficiency
   a VITAMIN K DEFICIENCY
   b *SEVERE HEPATIC DISEASE*
2 VITAMIN C DEFICIENCY
3 RENAL INSUFFICIENCY
4 BLOOD DYSCRASIAS WITH IMPAIRMENT OF THE NORMAL MECHANISMS FOR HEMOSTASIS
5 INTERRUPTIONS IN THE CONTINUITY OF THE VASCULAR SYSTEM
   a SURGICAL OPERATIONS
      i Recent operations on the brain and spinal cord
      ii Recent surgical operations leaving raw surfaces
      iii Postoperative tube drainage of wounds or viscera
      iv Operations performed in the presence of obstructive jaundice external biliary fistula or severe liver damage
   b ULCERATIONS AND OPEN WOUNDS
6 LATE PREGNANCY
7 SUBACUTE BACTERIAL ENDOCARDITIS

The more important clinical conditions which may lead to hypoprothrombinemia are listed in Table X

(a) Vitamin K Deficiency

The discovery that hypoprothrombinemia is associated with a deficiency of vitamin K was made when chicks were fed a diet extracted in such a manner that no fat soluble vitamins remained The chicks developed a hemorrhagic disease the manifestations of which were entirely the results of a diminished plasma prothrombin activity

Hypoprothrombinemia has not been produced in man by

and of fat soluble nutrients may be impaired or absent The deficient absorption of vitamin K leads to hypoprothrombinemia which accounts for the well known bleeding tendency encountered postoperatively in patients with obstructive jaundice or biliary tract fistula (245 248) If there is no significant liver damage this deficiency can usually be corrected promptly and efficiently by the administration of vitamin K and bile salts by mouth or by the parenteral administration of vitamin K without bile salts

Conditions which interfere with the digestion of fat may likewise interfere with the absorption of vitamin K Thus a depressed plasma prothrombin activity may be anticipated in those cases of pancreatic disease in which the supply of lipolytic enzymes to the intestine is interrupted (pancreatic steatorrhea) in tropical sprue (249) and in idiopathic steatorrhea (celiac disease non tropical sprue) (250 251) In the case of idiopathic steatorrhea with hypoprothrombinemia reported by Kark Souter and Hayward (251) the administration of vitamin K parenterally was followed promptly by an increase in the plasma prothrombin activity but this was not well maintained

A depletion of the vitamin K reserves of the body though not usually hypoprothrombinemia may occur when the normal absorbing surface of the intestine is deranged by disease or when the flow of intestinal content is either accelerated to a degree sufficient to interfere with absorption or interrupted Hypoprothrombinemia may thus occur in patients suffering from protracted vomiting or diarrhea from any cause in patients intubated for intestinal obstruction following surgical procedures such as gastrointestinal anastomoses resections and external fistulas and in cases of ulcerative colitis (252) regional ileitis and other chronic intestinal disease

(b) Severe Liver Disease (Deficient Synthesis of Prothrombin)

Severe liver disease which reduces hepatic function may interfere with the synthesis of prothrombin and thus be accompanied by hypoprothrombinemia This may in a sense be considered a defect in the utilization of vitamin K since in instances of extreme liver damage there is little or no response to the administration of vitamin K orally or parenterally

the simple restriction of vitamin K intake Kark and Lozner (242) have reported four instances of malnutrition and multiple vitamin deficiencies in which a mild hypoprothrombinemia was corrected by the administration of vitamin K Aggeler Lucia and Fishbon (243) have reported a case of severe anorexia nervosa with a marked hypoprothrombinemia which responded promptly to the administration of adequate amounts of vitamin K The possibility of depressed plasma prothrombin activity should be considered in all cases of pan avitaminosis The dietary restrictions of reducing diets and of the low fat diets so often prescribed to patients suffering from biliary tract and hepatic disease may lead if not to actual hypoprothrombinemia at least to a depleted reserve of vitamin K Hypoprothrombinemia is then apt to occur if such patients are operated upon

If chicks are kept on a diet free of vitamin K for a long period of time they will still not develop the characteristic hemorrhagic chick disease unless they are prevented from ingesting their feces (copraphagy) Vitamin K is present in the feces even when chicks are kept on a vitamin K free diet for a long period of time indicating that vitamin K is synthesized by the bacterial flora of the intestine Cited as further evidence that the vitamin is produced in the intestine are the results obtained by the administration of sulfaguanidine or sulfasuxidine (succinylsulfathiazole) to rats maintained on a diet deficient in vitamin K Whereas rats on a vitamin K deficient diet ordinarily do not develop a prothrombin deficiency those on such a diet to whom the sulphonamide is administered do develop a hypoprothrombinemia which can be corrected by the administration of vitamin K (241)

It has been suggested that hemorrhagic disease of the newborn is due to the inability of the relatively sterile gastrointestinal tract at birth to produce vitamin K It is possible for vitamin K deficiency to arise when the synthesis of vitamin K in the intestine is prevented by chronic intrinsic disease or by prolonged administration of the less readily absorbed sulfonamides in the treatment of such intestinal disease

When bile is excluded from the intestinal tract as in obstructive jaundice or in the presence of an external biliary fistula homogenization of fats does not occur and the absorption of fats

We have observed that very early liver damage can often be detected by the exaggerated response of the patient to a single dose of 200 or 300 mg of dicumarol Such an exaggerated response may occur in the absence of any abnormal response to the liver function tests ordinarily employed In certain instances this exaggerated response to dicumarol has been the only clue to hepatic dysfunction which has proved later to be on the basis of serious liver disease We concur therefore with the view that the response of a patient to dicumarol may serve as a sensitive index of prothrombin formation by the liver and as such is potentially a useful test of liver function Further studies correlating the response of patients with liver damage to dicumarol with the results of other liver function tests are necessary to evaluate this point

When initial doses of 200 to 300 mg of dicumarol are administered to patients who are extremely ill following an acute coronary occlusion with myocardial infarction the response is occasionally very much exaggerated so that within 24 hours the prothrombin clotting time may reach from 25 to 60 seconds (a reduction of prothrombin activity to from 25 to less than 5 per cent of normal) These patients usually die within 24 to 36 hours and do not present evidence of hemorrhage clinically Many of them exhibit severe congestive heart failure or profound shock In many instances the prothrombin clotting time before the administration of dicumarol is not prolonged The cause for this phenomenon is unexplained but an acute failure of the liver to produce prothrombin may be the explanation This type of response is probably of considerable prognostic significance and is certainly a contraindication to further anticoagulant therapy

(c) Miscellaneous Causes for Hypoprothrombinemia

Idiopathic Hypoprothrombinemia There have been a few instances reported of a chronic hypoprothrombinemia of unknown etiology apparently congenital resistant to vitamin K therapy and unrelated to any recognized hepatic dysfunction The findings of a prolonged coagulation time a normal bleeding time and the frequent occurrence of hemarthroses are similar to those of hemophilia and suggest that some of the cases reported as

Smith Warner and Brinkhous (253) observed a profound fall in the concentration of prothrombin in the blood of a dog after damaging the liver with phosphorus and chloroform Warner (254) accomplished the same result by performing partial hepatectomy in dogs Warren and Rhoads (255) and Andrus Lord and Moore (256) also have studied the effect of hepatectomy on the plasma prothrombin activity These experiments prove conclusively that the liver is essential to the maintenance of a normal plasma prothrombin level

Clinically hypoprothrombinemia occurs commonly in association with portal cirrhosis (257 258) primary and metastatic malignancy of the liver acute yellow atrophy fatty infiltration infectious hepatitis (catarrhal jaundice) and in cardiac cirrhosis A reduction in the prothrombin activity of the blood is found sufficiently often in cases of liver disease that the determination of the prothrombin clotting time and the response of the plasma prothrombin activity to the administration of vitamin K are utilized commonly as tests of liver function In this connection it must be remembered that a considerable amount of liver damage may exist before hypoprothrombinemia occurs

Unger and Shapiro (259) have devised a standardized test for liver function based upon the prothrombin response to the parenteral administration of large doses of vitamin K In instances of liver disease where the administration of vitamin K is ineffectual in restoring the prothrombin activity of the plasma to normal thus indicating that the liver is completely unable to synthesize prothrombin transfusions of fresh whole blood may increase the plasma prothrombin level temporarily

It is apparent that the anticoagulants particularly dicumarol must be used with great caution in the presence of vitamin K deficiency or liver disease In the presence of hepatic dysfunction irrespective of etiology the effect of dicumarol is unpredictable and the response of the prothrombin clotting time is both exaggerated and labile Although aberrations in response to dicumarol are more apt to occur when there is severe damage to the liver they may occur in relatively minor and reversible impairment of liver function such as occurs in chronic passive congestion secondary to congestive heart failure

addition of purified prothrombin or by the addition of either old or fresh human plasma Human plasma was consistently effective in controlling the patient s hemorrhagic tendency A positive cephalin flocculation test and the presence of a cryoglobulin in the patient s plasma suggest that there may have been a primary disturbance of protein synthesis in the liver

In the paper reporting this case Hagen and Watson have summarized in tabular form 13 cases of idiopathic hypoprothrombinemia previously reported by various observers With the possible exception of 1 patient to whom massive doses of vitamin K and large amounts of blood and plasma were given during a period of 3 days all of these cases were refractory to vitamin K although this was administered in small doses only in some instances

Lewis and Bennett (265) have reported a case of idiopathic hypoprothrombinemia in which there was a deficiency of Quick s component B The prothrombin time was prolonged to 10 minutes and the coagulation time of the whole blood to 60 minutes The fibrinogen content of the blood was normal The administration of massive doses of vitamin K resulted in a rapid return of the prothrombin time to normal and it had remained so for more than 60 days at the time of reporting The authors report that the administration of massive doses of Synkavite or of vitamin K_1 oxide will produce a rapid regeneration of component B unless there is severe liver damage

Hemorrhagic Disease of the Newborn (240) The newborn infant develops a deficiency of prothrombin at the time of or shortly after birth and this deficiency persists during the first 5 or 6 days of life The cause for the infant s apparent inability to synthesize prothrombin for this brief period is a matter of disagreement but usually the hypoprothrombinemia can be corrected promptly by the administration of vitamin K It may be prevented by the administration of vitamin K to the newborn at the time of birth or to the mother 12 to 24 hours before delivery

It is possible that the hemorrhagic disease of the newborn may be aggravated in the occasional infant to whose mother dicumarol is administered shortly prior to delivery Animal experiments cited in the section on pregnancy suggest that this hypopro

atypical hemophilia are in fact examples of idiopathic hypoprothrombinemia (241).

The first recognized case of idiopathic hypoprothrombinemia was reported by Rhoads and Fitz Hugh (260) in 1941. The familial nature of at least some of these cases was first indicated when Hauser (261) reported two families in which several members had prolonged prothrombin times.

A. J. Quick (91, 262, 263) has reported his observations on members of two families in which there is a chronic and apparently congenital prolongation of the prothrombin time. The syndromes in these two families appear to differ. In the first family the defect appears to be the same as that which occurs in the commonly known conditions of hypoprothrombinemia such as vitamin K deficiency and dicumarol poisoning. According to Quick's theory of the composition of prothrombin, members of this family are deficient in component B. The condition is truly congenital and familial. Bleeding does not occur. In the second family, component B is present but there is an absence of some additional factor and there is a definite hemorrhagic tendency. Quick designates this syndrome as congenital pseudohypoprothrombinemia.

Owren (107, 108) has reported detailed studies of the coagulation defect of a patient whose prolonged prothrombin time did not respond to vitamin K but which was restored to normal in vitro when 20 per cent prothrombin free ox blood was added to the patient's plasma. Owren proposed the term parahemophilia for this condition.

Hagen and Watson (264) have reported a case of idiopathic hypoprothrombinemia which has been followed in detail for a decade. The hemorrhagic syndrome in this instance included epistaxis, subcutaneous hematomas, periarticular hemorrhages, menorrhagia and metrorrhagia. Metrorrhagia was sufficiently severe as to necessitate hysterectomy. All available members of the family except the father showed a prolongation of the prothrombin time. The major deficiency in this patient was of Quick's component B, yet large amounts of vitamin K were not effective in shortening the prothrombin time. The prothrombin clotting time of the patient's plasma could be shortened in vitro by the

Histological examination of the livers of guinea pigs given dicumarol orally in doses of 25 mg every second day until death occurred irrespective of whether they had been maintained on a vitamin C free diet a normal diet or a diet fortified by the daily injection of 50 mg vitamin C showed a tendency to fatty infiltration and degeneration and a few foci of early necrosis An identical picture was observed in guinea pigs kept on a vitamin C free diet without administration of Dicumarol

As Link has recently stated although the effect of vitamin C on the response to dicumarol cannot be detected readily by the prothrombin test its influence in experimental animals on the extent and duration of hypoprothrombinemia and on the integrity of the capillary system cannot be ignored It is obvious that the administration of anticoagulants to patients suffering from vitamin C deficiency may be fraught with an increased risk of bleeding It is consequently suggested that all patients receiving anticoagulant therapy be given vitamin C

(3) Renal Insufficiency

Dicumarol must be administered cautiously if at all to patients with severe renal disease and renal insufficiency because the effect of dicumarol is exaggerated and prolonged in the presence of impaired renal function The reason for this is not clear In some cases of uremia there is evidence of liver damage and it has been postulated that certain end products of protein metabolism or their derivatives retained in the circulation produce a hepatotoxic effect If this is the case these toxic products may influence the plasma prothrombin activity directly or indirectly by interfering with the synthesis of prothrombin by the liver Uremia is also accompanied by an increased tendency toward bleeding and this tendency whatever its nature and its mechanism of production will certainly aggravate the tendency of the anticoagulants to produce bleeding

Another reason for the cautious use of anticoagulants in the presence of renal disease is the relatively high incidence of hematuria among the hemorrhagic manifestations of anticoagulant therapy particularly of dicumarol but to a lesser extent of heparin also This aspect of the problem is discussed in a subse

thrombinemia may be aggravated in the breast fed infant if the mother receives dicumarol during the period of breast feeding

Shock (240) A significant prolongation of the prothrombin time occurs in certain instances of traumatic and hemorrhagic shock in man The mechanism of its production is not known

The effect of certain drugs on the plasma prothrombin activity will be discussed in a later chapter

(2) VITAMIN C DEFICIENCY

Although the role of vitamin C in the maintenance of hemo*stasis is concerned primarily with the integrity of the capillaries presumably by regulating in some manner the deposition of inter*cellular cement and while it is not generally considered to be implicated in the process of blood coagulation there is some experimental evidence that a deficiency of vitamin C may influence the hypoprothrombinemia induced by dicumarol

Link and his associates (266 267) studied the effect of vitamin C on the action of dicumarol They found that when high levels of 2 methyl 1 4 napthoquinone and l ascorbic acid are given to rabbits simultaneously the combined action either drastically reduces or completely nullifies the action of a single dose of dicumarol They showed subsequently that the administration of l ascorbic acid to rats fails to alter either the degree or duration of the hypoprothrombinemia induced by dicumarol but that substances which stimulate the synthesis of vitamin C in the rat (e g carvone and chloretone) markedly reduce the degree of hypoprothrombinemia induced by dicumarol

Sullivan and Gangstad (268) demonstrated that in the guinea pig massive doses of l ascorbic acid prolong the survival time of animals receiving small daily doses of dicumarol and that when a single dose of dicumarol is given to guinea pigs depleted of vitamin C the degree of hypoprothrombinemia is increased and the duration drastically prolonged Finally Richards and Cortell (156) confirmed the observation of Sullivan and Gangstad that vitamin C depleted guinea pigs tend to succumb earlier to large doses of dicumarol than do animals receiving normal or vitamin C supplemented diets

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quent chapter devoted to the hemorrhagic manifestations of anti coagulant therapy

(4) Blood Dyscrasias with Impairment of the Normal Mechanisms for Hemostasis

Increased bleeding may follow the administration of anti coagulants to patients with purpuras or to those with blood dyscrasias in which the normal mechanisms for hemostasis are impaired or lost As a rule the plasma prothrombin activity is normal in the presence of such blood dyscrasias as the leukemias thrombocytopenic purpura and aplastic anemia (239) However these diseases are accompanied frequently by an increased tendency to bleed and there is some evidence that this hemor rhagic tendency may be due to the release into the circulation of heparin (321)

Polycythemia vera presents a special problem Although it is essentially a hematogenous disease it frequently presents itself by the development of occlusive vascular disease particularly arterial occlusions or thrombophlebitis At the same time there may be also an associated tendency to increased bleeding Thus though anticoagulant therapy is indicated for the treatment of the vascular occlusive disease it must be administered with great caution The prothrombin level in these patients is subject to unusual fluctuations during dicumarol therapy

(5) Interruptions in the Continuity of the Vascular System

Surgical Operations

When the continuity of the vascular system is interrupted by accidental trauma or by surgical operation the administration of an anticoagulant may be followed by local hemorrhage Such hemorrhage may be confined to the wound or operative tract or it may dissect into the tissues or pour out onto the surface of the body Probably the majority of such hemorrhages which are discovered are those which make their appearance as subcutaneous hematomata

Particularly serious however are those massive hemorrhages which occur into the hollow viscera or into the serous cavities or which dissect into the various solid viscera or their supporting tissues Such hemorrhages are often not recognized during life

and are discovered only at postmortem examination Although minor hemorrhages probably cannot be avoided in a certain minority of surgical cases *serious postoperative hemorrhages are infrequent when surgical hemostasis is observed meticulously*

The use of heparin immediately following surgical operations is accompanied by a rather high incidence of hemorrhages and it is probably advisable to defer the administration of heparin for several hours postoperatively Among 351 patients to whom Crafoord (32) administered heparin postoperatively there were but 2 serious hemorrhages The first of these was a retroperitoneal hematoma which occurred in a woman age 70 who had had an ileocecostomy for cancer of the colon The patient died on the 3rd day with signs of heart failure and autopsy revealed 800 cc blood in the peritoneal cavity In a 2nd patient the enucleation of a myoma was followed by the development of symptoms of peritoneal irritation on the 2nd postoperative day An exploratory laparotomy revealed a peritoneal hematoma The patient recovered after several transfusions had been given

Wetterdal observed moderate bleeding in 4 patients out of 231 postoperative patients to whom heparin was administered post operatively One patient developed a retroperitoneal hematoma between the bladder and the vagina which required surgical exploration and repeated transfusions A second similar hemorrhage occurred 3 weeks later in the absence of heparin A 2nd patient age 38 had a supravaginal hysterectomy for myomata Despite her poor postoperative condition heparin was started on the 3rd day The patient s condition deteriorated and she died in uremia Postmortem examination revealed 1400 cc of bloody exudate in the peritoneal cavity

By reasons of its delayed effect on the plasma prothrombin time dicumarol even when administered immediately after operation might be expected to produce fewer postoperative hemorrhages than does heparin Allen Barker and Hines (65) report that bleeding from wounds occurs occasionally but that in their experience it had not been critical in any instance and has always been controlled They cite statistics for 1 000 patients treated postoperatively with dicumarol Minor bleeding occurred in 39 (3 9 per cent) major bleeding in 25 (2 5 per cent) of these patients

Cheney (269) has reported in detail an instance of gastroin

testinal hemorrhage which followed the administration of dicumarol to a patient recovering from vagotomy and a subtotal gastric resection for duodenal ulcer On the 4th postoperative day the patient developed an acute femoral thrombophlebitis and on the 7th postoperative day dicumarol was started On the 11th postoperative day 4 days after dicumarol was begun severe gastrointestinal hemorrhage was manifested by pallor weakness and the passage of tarry stools Tarry stools continued for 6 days and there was vomiting of 100 cc bright red blood on the 14th postoperative day Transfusions were given repeatedly but vitamin K only once in a single dose of 20 mg The patient experienced an uneventful recovery thereafter

Butsch and Stewart (270) and Laufmann and Heller (200) have reported that wound healing is not impaired by the administration of heparin while Sandblom (271) and Bruzelius (272) have found that dicumarol does not interfere with healing unless the plasma prothrombin activity is very much reduced

There are certain types of operations operations in certain locations and operations performed under certain circumstances which are especially prone to hemorrhage following the administration of anticoagulants and which provide a special hazard These are enumerated as follows

1 Operations on the brain or spinal cord because even a small amount of bleeding may be disastrous
2 Operations such as prostatectomies guillotine amputations and amputations of the breast which leave extensive raw surfaces
3 Massive resections especially those of the gastrointestinal tract for malignancy ulcer bowel obstruction mesenteric thrombosis and the like
4 Operations followed by tube drainage of wounds or of hollow viscera
5 Operations performed in the presence of obstructive jaundice external biliary fistula or severe liver disease (239 245 248)

If a surgical operation is contemplated in a patient receiving anticoagulant therapy the anticoagulant must be discontinued in sufficient time to permit the influence of the drug to wear off or if an emergency operation is necessary the effect of the anticoagulant must be counteracted by the use of the proper antagonist

vitamin K and fresh whole blood transfusion for dicumarol and protamine sulfate or toluidine blue for heparin The use of heparin in vascular surgery has been referred to previously and is discussed in detail in the papers of Murray (34 55 166 201 204) and in the text by Jorpes (32)

Ulcerations and Open Wounds

Ulcerations wounds and raw surfaces from any cause on the skin or on the mucous membranes may be the source of hemor rhage following the administration of anticoagulants Gross hemorrhage from the gastrointestinal tract of man has occurred occasionally in patients with peptic ulcer hiatal hernia hemor rhoids gastrointestinal neoplasms and certain intestinal diseases when anticoagulants have been administered Bleeding into the site of a fracture following the administration of an anticoagulant has occurred One frequently expressed fear of the use of the anticoagulants on an ambulatory basis is the risk of exaggerated hemorrhage occurring as a complication of accidents or trauma which may befall the patient during the period over which his prothrombin activity is reduced We are not aware that any instances of this sort have been reported in the literature

Leedham and Orbison (273) have observed an instance of cardiac tamponade associated with the administration of dicumarol to a patient who had suffered multiple severe injuries in an aircraft accident In addition to multiple lacerations and multiple fractures this patient had sustained severe vascular injury to the right lower leg and the right foot was ischemic There was gross hematuria There was no clinical or radiological evi dence of injury to the thoracic cage or its content Intensive therapeutic measures were undertaken to save the foot including the administration of dicumarol beginning on the 8th hospital day At this time there was clinical and electrocardiographic evi dence of an acute pericarditis which was interpreted as a traumatic pericarditis or contusion of the heart By all evidence available this process had subsided on the eighteenth day

On the 19th day after 700 mg of dicumoral had been ad ministered over a period of 10 days symptoms and signs of an acute cardiac tamponade appeared suddenly This was confirmed by x ray and by electrocardiogram Pericardial aspiration removed

380 cc of dark non clotting blood from the pericardial sac with immediate relief of symptoms The prothrombin clotting time at the onset of the acute tamponade was 79 seconds (prothrombin activity 5 per cent of normal) Two 500 cc transfusions of fresh whole blood and 256 mg of Hykinone were given during the subsequent 18 hours The prothrombin time was reduced to 40 seconds (prothrombin activity of 11 per cent) after 24 hours and to 26 seconds (prothrombin activity of 22 per cent) after 48 hours There was a transient microscopic hematuria during this time There was no evidence of further bleeding into the pericardial sac

(6) Late Pregnancy

Heparin has been administered successfully to women during pregnancy for the treatment of thromboembolic conditions and in a few instances for the treatment of toxemia of pregnancy (187 188) Barnes and Ervin (271) have reported that the blood loss during the puerperium is not increased by the administration of heparin or of dicumarol during this period Leissner (275) has attempted to initiate prophylactic heparinization of patients as early as 2 hours after delivery but serious uterine hemorrhage occurred in his 4th patient and he did not begin heparin until 12 to 24 hours postpartum in subsequent patients Jorpes states that the usual Scandinavian practice in using heparin prophylactically during the puerperium is to begin the drug 48 hours after childbirth

Greene and Loewe (276) state that their experience with heparin/Pitkin menstruum in the obstetric wards may well suggest its ultimate adoption as a prepartum prophylactic measure However of the 34 cases of thromboembolic disease complicating the puerperium treated by them only one was treated before delivery Heparin therapy was interrupted during labor and was restarted postpartum

It has been reported repeatedly that the prothrombin activity of human plasma is usually increased during the later stages of pregnancy (274 277 279) Davis and Porter (280) have reported favorably on the treatment of puerperal thrombophlebitis with dicumarol and state that they have not observed any instances of gross hemorrhage in their patients

Field and his associates (281 282) have made some interesting

experimental observations on the relation of pregnancy and lactation to the anticoagulant effect of dicumarol They observed that pregnant and lactating rats tolerate higher doses of dicumarol than do normal female rats Continuous feeding of the anticoagulant to female rats with suckling pups caused the pups to become hypoprothrombinemic and subject to hemorrhage The administration of vitamin K showed a greater protective effect on the pup than on the mother These observations were later confirmed on the dog

Allen has suggested that caution be exercised in the administration of dicumarol to the postpartum patient He states that there is little risk of bleeding after the 7th day if the uterus has involuted properly and the lochia is normal v Sydow (283) has reported an instance of hypoprothrombinemia and cerebral injury in a newborn infant after the mother had been treated antepartum with dicumarol for venous thrombosis

Kraus Perlow and Singer* observed the influence of dicumarol on the intrauterine growth and development of the fetus in pregnant rabbits The prothrombin time was determined by Quick s method using a thromboplastin prepared from rabbit s brain The newborn of four pregnant rabbits who did not receive any dicumarol and whose prothrombin times were normal suffered a depression of prothrombin activity during the first 24 hours following birth

Four pregnant rabbits were given sufficient dicumarol to depress prothrombin activity to less than 10 per cent of normal for no more than a few days at a time When such low values were attained dicumarol was withheld but no vitamin K was given The pregnant rabbits whose prothrombin levels were reduced to below 10 per cent at one time or another during pregnancy died Only one fetus survived to the time of delivery and this was in a rabbit which received dicumarol only during the last week of gestation The fetuses were small macerated and decomposed

Four pregnant rabbits were given dicumarol in amounts to maintain safe prothrombin levels Three of the four pregnant rabbits survived and did not bleed excessively at any time The newborn sustained an extreme depression of their prothrombin

* Kraus A P Perlow S & Singer K Danger of dicumarol treatment in pregnancy *J A M A* 139 758 762 (March 19) 1949

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SECTION V

TECHNICS FOR THE ADMINISTRATION OF THE ANTICOAGULANTS

levels at the time of birth The newborn exhibited a pronounced hemorrhagic tendency and none survived for more than five days A few fetuses were stillborn

These experiments indicate that dicumarol passes the placental barrier *One out of four pregnant rabbits with* safe prothrombin levels aborted on the 21st day and died 5 days later The newborn demonstrated (1) extreme depression of prothrombin activity (2) *definite hemorrhagic tendency and (3) death prior to or shortly* after birth The prothrombin depression in these newborn was more pronounced than that seen following birth in normal rab bits Toxic doses of dicumarol consistently produced intrapartum hemorrhage and postpartum death of the mothers The fetuses of only one rabbit in this group survived to the time of delivery

These and our own observations indicate that if anticoagulants are to be administered to pregnant women especially to those approaching term considerable caution must be exercised Not only is there the risk that the patient will hemorrhage profusely at the time of delivery or thereafter but in the case of dicumarol there is a serious risk that the infant will suffer hemorrhages during the process of delivery or during the first week of life Suggestions for the management of this problem are included in the chapter on the management of hemorrhages due to anticoagulants

(7) SUBACUTE BACTERIAL ENDOCARDITIS

The use of heparin as an adjunct to the treatment of subacute bacterial endocarditis with penicillin has been largely abandoned (175 177) *The use of dicumarol is felt to be contraindicated* in cases of subacute bacterial endocarditis since it may increase the risk of hemorrhage which is inherent to this disease

It should be emphasized that the number of cases to whom anticoagulants should not be administered will vary in inverse proportion to the experience of the physician administering the drug It is the experience of those investigators who have used both heparin and dicumarol over a period of some years that these drugs may be administered safely to patients suffering from many of the conditions *discussed in this chapter if painstaking attention* is paid to the patient s condition and to his plasma prothrombin clotting time

CHAPTER 12

The Administration of Heparin

HEPARIN a polysaccharide containing glucosamine an uronic acid and sulfuric acid esters is a normal constituent of the mammalian body It has been accepted quite generally but not universally that heparin is formed in the mast cells of Ehrlich which are particularly numerous in the perivascular connective tissue (32)

Heparin is not effective when given orally but it is effective by all of the usual routes of parenteral administration Heparin must interfere with the first stage of clotting since prothrombin is present unchanged in heparinized blood (284) but it has also an effect on the second stage of clotting its so called antithrombin action (146) The anticoagulant action of heparin is manifested by the prolongation of the coagulation time of the whole blood and its effect is measured with sufficient accuracy for clinical purposes by the determination of the clotting time of whole blood in a test tube by the method of Lee and White (132)

Advantages and Disadvantages of Heparin

The advantages of heparin as an anticoagulant are numerous It may be administered by all of the various routes for parenteral administration—intravenously by intermittent injection or by continuous drip subcutaneously in aqueous solution or in Pitkin menstruum intramuscularly in concentrated or dilute aqueous solution or suspended in oil or gelatin or intrasternally (32) Its effect in prolonging the coagulation time of the whole blood is prompt a matter of minutes This effect diminishes over a period of 3 to 4 hours except when heparin has been administered in a menstruum which releases it slowly Finally the effect of heparin on the coagulation time can be determined conveniently at the bedside

However heparin has 2 disadvantages which are very definite

longation for the duration of therapy This is generally achieved if 300 000 mg of heparin are added to a liter of 5 per cent glucose and administered at a rate of 15 to 25 drops per minute for the entire 24 hours Between 15 and 25 mg of heparin are administered per hour and the total amount of fluid introduced per 24 hours is about 1200 cc

When heparin is given by continuous drip the clotting time of the whole blood should be determined ordinarily at intervals of every 2 to 3 hours since longer intervals without testing are unsafe and have resulted in fatalities If heparin is administered to a patient by this method immediately after operation the coagulation time should be determined every hour for the first 24 hours because of the increased hazard of bleeding if the coagulation time is greatly prolonged The rate of flow of the infusion should be regulated carefully and frequently Ordinarily it should be increased or decreased by no more than 2 to 4 drops per minute at any single adjustment as indicated by the periodic determination of the coagulation time The number of drops falling per minute should be counted at frequent intervals and the flow regulated to the desired rate with great care

Heparin/Pitkin Menstruum

Leo Loewe and his associates (51 170 195 196 276 285 288) and Evans and Boller (289) have advocated the use of heparin given subcutaneously in Pitkin s menstruum with or without the addition of vasoconstrictors (epinephrine and ephedrine) They have had a very great experience with this mode of administering heparin and report consistently favorable results The ingredients of the Pitkin menstruum are gelatin dextrose glacial acetic acid and distilled water Since the rate of liberation of the contained heparin is inversely proportional to the viscosity of the menstruum the constituents are in proportions calculated to produce an optimal viscosity

Heparin in Pitkin menstruum is distributed in ampules containing 200 mg or 300 mg of the sodium salt of heparin Ampules labelled with vasoconstrictors contain ephedrine sulfate and epinephrine hydrochloride intended to delay the absorption of the heparin and thus prolong the anticoagulant effect The use

handicaps to its use clinically Heparin is very expensive and it cannot be administered by mouth

Intravenous Heparin

Heparin is most commonly administered intravenously and by the intermittent injection of the sodium salt dissolved in saline diluent in a concentration of 10 mg per cc (32 65 174) Injections are made at intervals of from 3 to 6 hours most commonly at 4 hours In The New York Hospital the procedure is generally as follows

> If a preliminary determination of the clotting time of the patient s whole blood reveals a normal value i e 4 to 8 minutes 50 mg of sodium heparin in 5 cc of saline is injected intravenously and the clotting time is determined at intervals of approximately 1 hour for the first 4 hours The clotting time should be prolonged to from 30 to 60 minutes at the peak of effectiveness and it should not have returned to from 10 to 15 minutes until 3 to 4 hours have elapsed Depending upon the response of the patient to this initial dose 50 to 75 mg of heparin are administered intravenously every 4 hours thereafter and *the clotting time is determined immediately preceding each subsequent injection,* during at least the first few days

Many Scandinavian physicians do not check the clotting time of the blood of patients under the influence of heparin with any degree of regularity and in some instances not at all feeling that the response is sufficiently consistent as to make this test unnecessary However it is our belief that the clotting time should be determined on several occasions during each day until the response of the particular patient is clearly determined

Heparin in physiologic saline in 5 per cent glucose solution or in distilled water may also be administered intravenously to bedridden patients by continuous drip (32 64) There has been some question as to the advisability of using this method with patients in cardiac or renal failure because large amounts of saline are often injected but this may be avoided easily by using a fluid free of sodium salts The objective in administering heparin by continuous drip is to prolong the clotting time of the blood to from two to four times normal and to maintain this pro

is heparin in Pitkin menstruum but acts otherwise in a similar manner It appears to be particularly useful as a means of administering heparin during the first few days of combined heparin dicumarol therapy—until dicumarol is effective We have found that the administration of 200 mg twice a day is a satisfactory dosage schedule for most patients A clotting time by the method of Lee and White should be done before each dose is given If the clotting time exceeds 20 minutes the dose should be postponed for six hours or omitted Use of this preparation each day for more than 5 or 6 days is not recommended until the preparation has been more fully evaluated

Concentrated Aqueous Heparin

Heparin may be administered intramuscularly dissolved in an aqueous medium for prompt absorption or suspended in an oily menstruum for delayed absorption (290 292) Those who have used heparin in these media and by this route claim that injections are less painful than is the injection of heparin in Pitkin menstruum Intramuscular injection is preferred not only because it is less painful than is subcutaneous injection but because absorption is more regular

The paucity of reports on clinical experience with the intramuscular injection of dilute heparin suggests that the experience with it has been unsatisfactory A disadvantage which is apparent immediately is that a relatively large volume of solution must be injected with each dose since each cc of solution or suspension contains only 10 mg of heparin

Stats and Neuhof (173 293) have administered successfully by intramuscular injection a concentrated solution of heparin containing 100 mg of heparin per cc They claim that preparation free of vasoconstrictors or foreign substances fulfills the requirements for simple painless safe and readily controlled administration

Neuhof (173) has reviewed briefly more than a year's experience with concentrated aqueous heparin administered to over 100 cases The concentrated heparin is injected into the gluteal muscles in the conventional manner at intervals of from 8 to 12 hours A prolongation of the coagulation time is evident within

of heparin sodium with vasoconstrictors should be avoided in patients *with hypertension or myocardial disease and also in cases* of arterial occlusion by thrombus or embolus to avoid aggravating the existing arterial spasm

I oewe ordinarily administers an initial dose of 300 mg of sodium heparin to *patients weighing up to 150 pounds* and 400 mg to patients weighing more than this Subsequent doses are administered to maintain the clotting time at between 30 and 60 minutes as determined by the Lee White method The conventional dose of 300 mg of heparin will be satisfactory for about 90 per cent of patients The remaining 10 per cent are either hypo or hyperreactors and will require doses of 400 or 200 mg respectively In the average patient a single dose of one 3 cc ampule containing 300 mg heparin sodium will suffice to produce an adequate heparin effect for approximately 2 days In such a patient the content of one 3 cc ampule is administered every 2nd day for the duration of therapy

If a blood transfusion is given the patient during this time one 3 cc ampule of heparin sodium in Pitkin menstruum should be administered immediately thereafter irrespective of previous injections In the presence of a very severe thromboembolic tendency 400 to 500 mg of heparin in Pitkin s menstruum is given and an attempt is made to prolong *the clotting time to* from 1 to 2 hours When vasoconstrictors are indicated and more than 1 ampule is to be administered at a given time use only 1 ampule containing vasoconstrictors The amount of vasoconstrictor drugs in one ampule is sufficient for an entire dose of heparin

In our experience heparin in Pitkin menstruum is excessively painful and the patients frequently refuse a 2nd injection Likewise the response of the clotting time of the whole blood to this form of administration has been very irregular and unpredictable Efforts are being made to produce a more satisfactory menstruum

We have recently had experience with Depo Heparin Sodium [1] a preparation of 200 mg of heparin sodium with or without vasoconstrictors per cc of a gelatin dextrose *medium This* preparation appears to be much less painful upon injection than

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[1] The Upjohn Company

much as 300 mg may be concentrated in as little as 0 1 cc of solution

It has been suggested recently that caronamide may be useful in delaying the excretion of heparin and thus permitting the more economical administration of this anticoagulant (295) Since with doses of heparin sufficient to produce moderate blood levels only a small portion of the injected heparin is excreted (146) it does not seem likely that caronamide will significantly reduce the amount of heparin required for therapeutic purposes

one half to 1 hour after the initial injection reaches a maximum (30 to 60 minutes) in from 4 to 6 hours after injection and approaches normal in about 8 to 12 hours after injection Individual doses of concentrated aqueous heparin vary from 50 to 180 mg correlating roughly with the weight of the patient Adequate heparinization of patients weighing less than 130 pounds is attained by the injection of 100 mg every 8 hours or by the injection of from *120 to 140 mg* every *12 hours* Proportionately larger doses are used for heavier individuals The maximum daily dose should not exceed 450 mg

Stats and Neuhof (293) state that the effect of heparin administered in this manner is controlled with ease and that a single determination of the coagulation time before the injection of the first daily dose is sufficient The dose for the day is reduced slightly if the coagulation time in the morning is found to be over 24 minutes Small hematomata and slightly painful nodules have been noted at the site of injection occasionally No published reports confirming this experience have come to our attention

Vorzimer Sussman and Marder (294) have been able to prolong the coagulation time to from 200 to 900 per cent of normal for 17 to 24 hours with a single intramuscular injection of concentrated heparin (200 mg per cc of aqueous solution) emulsified in 1 cc of a mixture of cholesterol derivatives (35 per cent) peanut oil (65 per cent) and beeswax (2 per cent) Approximately 1 25 to 2 0 mg of heparin per pound of body weight was necessary to maintain this effect The sustained action of heparin was assured when the volume of the menstruum and the volume of heparin solution were kept equal There was no hemorrhage at the site of injection and pain was negligible No bleeding occurred and there were no toxic effects Injections of the menstruum alone produced no effect on the coagulation time and injections of 1 cc of the aqueous solution of heparin (200 mg) produced a prolongation of the coagulation time of only 6 hours duration

It is worthwhile to remember that heparin is an extremely soluble substance and that it can be administered clinically in concentrations considerably greater than have hitherto been attempted *Although* it is not known if it would be desirable as

inactivated or destroyed For this reason when the immediate hazard of thromboembolism is great heparin should be administered concurrently for the first 2 or 3 days to protect the patient during this initial latent period

When dicumarol is *withdrawn* its effect on the prothrombin time persists for from 2 to 7 days (39 296 298) If a hemorrhagic complication occurs during the administration of dicumarol or if the anticoagulant effect of the drug must be terminated promptly for some other reason it is necessary to invoke active measures to antagonize the effect of dicumarol

The response of different individuals to given doses of dicumarol is not accurately predictable and the response of the same individual is often unpredictable from day to day *necessitating the daily determination of the prothrombin clotting time before each dose of the dicumarol is given* at least during the initial phase of the treatment and until the response of the patient to the drug has been studied thoroughly

The expense of performing a prothrombin test every day reduces to some extent the economic advantage of dicumarol but when a patient who is receiving dicumarol has been under observation for a time and appears to respond in a reasonably predictable manner it is frequently possible to perform the prothrombin test at intervals greater than every day The test may then be performed on alternate days and gradually at longer intervals up to 1 week The determination of the prothrombin time at intervals greater than every other day should not be attempted unless the physician has had an extensive experience with the drug

It is evident that the use of dicumarol requires painstaking and continuous supervision of the patient and of the laboratory findings during the entire period of anticoagulant therapy even though this therapy may be continued for weeks months or years

The Determination of the Plasma Prothrombin Clotting Time

The importance of the laboratory control of dicumarol therapy must be understood clearly by any physician who wishes to use

CHAPTER 13

The Administration of Dicumarol

IT IS believed that dicumarol 3 3 methylenebis (4 hydroxy coumarin) produces an anticoagulant effect by suppressing the formation of prothrombin in the liver Its effect is reflected in the prolongation of the prothrombin clotting time of the plasma As discussed previously in Chapter 8 it does not consistently prolong the clotting time of the whole blood as determined in glass tubes by the Lee White method when administered in ordinary therapeutic doses (148)

Advantages and Disadvantages of Dicumarol

Dicumarol has 2 great advantages over heparin—it is cheap and it is effective when administered orally There is however no commercial preparation of dicumarol for parenteral administration Opinion is divided as to which anticoagulant is more easily administered and more readily controlled depending largely upon the experience of the individual using the drug After more than a decade of experience with heparin and 8 years of experience with dicumarol (I S W) we favor the latter for general use provided that proper laboratory control is available However we use both drugs in daily practice according to the indications in a given case

Dicumarol has however certain disadvantages Since a single dose of dicumarol does not produce its maximum effect as measured by the prolongation of the prothrombin clotting time for from 48 to 72 hours the patient to whom it is administered is not fully protected during the early portion of this period of time following the initial dose (39 296 298) This is presumably due to the fact that dicumarol interferes with the synthesis of prothrombin but has no effect upon prothrombin which has already been formed The latent period represents the period of time necessary for the circulating plasma prothrombin to be

and to minute variations in technic and concentrations of reagents that using the same method and the same thromboplastin significant variations in results may be obtained by different laboratories or even in the same laboratory from time to time

The clinician must understand the mechanism of the test and the potential causes for the variations which may be encountered to interpret the values reported to him by a specific laboratory on samples of blood submitted from a given patient He must know what modification of the method is being used what thrombo plastin is being used and what values are obtained when the prothrombin clotting times of normal whole plasma and of normal diluted plasma are determined daily as controls

The prothrombin clotting time is determined in our laboratory by the Link Shapiro modification of the one stage method (299 306 307) utilizing a thromboplastin extracted from rabbit lung (Cf *Appendix D*) When performed on samples of whole plasma (undiluted plasma) from normal persons (i e persons whose plasma is presumed to possess normal prothrombin activity) values of from 14 to 17 seconds are obtained consistently Only rarely do the values fall slightly outside of this range The pro thrombin clotting time is also determined routinely on samples of plasma which have been diluted to 12 5 per cent of normal with 0 85 per cent saline (dilution of 1 8) and in normal persons values of 38 seconds $\pm$ 5 seconds are obtained with these diluted plasmas

If the technic of performing the prothrombin clotting time is altered or if the thromboplastin is obtained from a different source or extracted in a different manner the values obtained with normal plasma whether whole or diluted will differ slightly from those just quoted Under such circumstances the quoted figures which serve as daily controls may no longer be reliable standards of comparison for the values obtained on samples of plasma from patients being treated with dicumarol A new and different set of control values must be obtained by determining the prothrombin clotting time on normal persons by the different technic or with the different thromboplastin

Not only may thromboplastic reagents which are prepared in different laboratories differ in potency but various lots of throm

the drug is an anticoagulant There are many unanswered or unsatisfactorily answered questions relative to the effect of dicumarol on the prothrombin clotting time but if the results of the test are interpreted cautiously it serves as an adequate guide to the administration of dicumarol in the great majority of cases

There are in general 2 methods for performing a prothrombin test namely the one stage method first described by A J Quick (89) (Cf *Appendix B*) and subsequently modified in certain respects by other investigators and the two stage method of Warner Brinkhous and Smith (97) (Cf *Appendix C*) The latter method is an excellent research tool but is not as widely used for clinical purposes as is the one stage method because of its somewhat greater complexity and the further amount of work involved We will therefore discuss only the one stage method in detail

The One Stage Method

In outline the one stage prothrombin test is performed by adding to a sample of oxalated or citrated blood plasma an excess of ionic calcium and an excess of thromboplastin and then determining the time necessary for the plasma to clot The test is based on the concept that if you have an excess of calcium and of thromboplastin in the coagulation system the speed of clotting will vary in proportion to the concentration of prothrombin in the sample of plasma It is recognized that the actual facts are more complex than this simple explanation and that the test probably measures something more than prothrombin alone but we continue to use this test because when performed correctly it provides the best available guide for clinical work and because without such a test we cannot use dicumarol either safely or effectively

The use of the one stage method for determining the prothrombin clotting time is complicated by several important factors which must be considered in the interpretation of the results obtained First there are several modifications in the technic of performing the test (299 301) Secondly there are a variety of thromboplastic reagents obtained from quite different sources which can be used in performing the test (302 305) Finally the test is sufficiently sensitive to a variety of environmental conditions

and to minute variations in technic and concentrations of reagents that using the same method and the same thromboplastin significant variations in results may be obtained by different laboratories or even in the same laboratory from time to time

The clinician must understand the mechanism of the test and the potential causes for the variations which may be encountered to interpret the values reported to him by a specific laboratory on samples of blood submitted from a given patient He must know what modification of the method is being used what thromboplastin is being used and what values are obtained when the prothrombin clotting times of normal whole plasma and of normal diluted plasma are determined daily as controls

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Not only may thromboplastic reagents which are prepared in different laboratories differ in potency but various lots of throm

the drug as an anticoagulant There are many unanswered or unsatisfactorily answered questions relative to the effect of dicumarol on the prothrombin clotting time but if the results of the test are interpreted cautiously it serves as an adequate guide to the administration of dicumarol in the great majority of cases

There are in general 2 methods for performing a prothrombin test namely the one stage method first described by A J Quick (89) (Cf *Appendix B*) and subsequently modified in certain respects by other investigators and the two stage method of Warner Brinkhous and Smith (97) (Cf *Appendix C*) The latter method is an excellent research tool but is not as widely used for clinical purposes as is the one stage method because of its somewhat greater complexity and the further amount of work involved We will therefore discuss only the one stage method in detail

The One Stage Method

In outline the one stage prothrombin test is performed by adding to a sample of oxalated or citrated blood plasma an excess of ionic calcium and an excess of thromboplastin and then determining the time necessary for the plasma to clot The test is based on the concept that if you have an excess of calcium and of thromboplastin in the coagulation system the speed of clotting will vary in proportion to the concentration of prothrombin in the sample of plasma It is recognized that the actual facts are more complex than this simple explanation and that the test probably measures something more than prothrombin alone but we continue to use this test because when performed correctly it provides the best available guide for clinical work and because without such a test we cannot use dicumarol either safely or effectively

The use of the one stage method for determining the prothrombin clotting time is complicated by several important factors which must be considered in the interpretation of the results obtained First there are several modifications in the technic of performing the test (299 301) Secondly there are a variety of thromboplastic reagents obtained from quite different sources which can be used in performing the test (302 305) Finally the test is sufficiently sensitive to a variety of environmental conditions

compared directly with the results obtained in other laboratories or by other technics or with different thromboplastin Actually it has not been demonstrated convincingly that conversion to per cent of prothrombin activity does permit exact comparison It does permit sufficiently satisfactory comparison for clinical purposes However an error in technic which affects the prothrombin

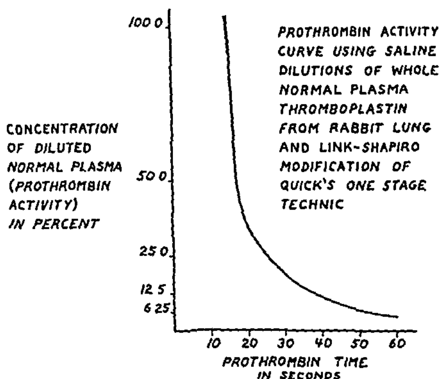


FIGURE 15 Prothrombin Activity Curve

time in seconds will be perpetuated not corrected by conversion of the value into per cent

Since the reporting of prothrombin clotting times in seconds permits the clinician to observe that the control value for the day is within the range ordinarily obtained by the particular laboratory and so affords him some assurance as to the reliability of the technic and the potency of the thromboplastin the daily report from the laboratory should always include both the patient s prothrombin time and the control prothrombin time in seconds

boplastin prepared in the same laboratory may vary in potency from day to day. Thromboplastin must be stored in a refrigerator at zero degrees Centigrade to prevent a progressive loss of potency.

To be able to interpret reliably the prothrombin clotting time reported on a patient receiving dicumarol, it must be compared with the control value for the given day. This value may vary by as much as 3 or 5 seconds from day to day when whole plasma is used, by as many as 10 seconds when 12.5 per cent diluted plasma is used, depending upon differences in technic and upon the potency of the thromboplastin. Experience in performing the prothrombin clotting time will lead to more exacting and reproducible technic, but the potency of the thromboplastin will vary from lot to lot. It must therefore be checked for potency at the time it is used.

Prothrombin Activity Curve

It is customary for a laboratory performing tests of the prothrombin clotting time to derive what is known as a "prothrombin activity curve," which is used to convert the prothrombin clotting time in seconds to the "prothrombin activity" in per cent. This curve is obtained by determining the prothrombin clotting time of normal whole plasma and of normal whole plasma diluted to 50, 25, 12.5 and 6.25 per cent. The values in seconds so obtained are then plotted against the concentrations of the plasma expressed in per cent. Such a "prothrombin activity curve," erected in our own laboratory by using the technic and the thromboplastin previously specified, is reproduced in Figure 15. By the use of such a curve, the results of the prothrombin clotting time may be reported in terms of "percent of prothrombin activity" rather than directly in observed seconds. This requires an assumption that the reductions in prothrombin activity produced by diluting the normal whole plasma with the saline represent, at least roughly, the reductions in prothrombin activity produced by administering dicumarol to a patient.

Prothrombin activity curves are utilized so that the temporal values obtained by performing the prothrombin clotting time in 1 laboratory or by 1 method or with 1 thromboplastin can be converted into per cent of prothrombin activity and then

time on the particular day the response of the patient to previous doses and the trend of the prothrombin level whether upward or downward

5 If the prothrombin time (as determined in our laboratory by the Link Shapiro modification of the one stage technic using thromboplastin made from rabbit lung) is shorter than 30 seconds (equivalent to a prothrombin activity greater than 20 per cent of normal) 100 to 200 mg of dicumarol are given

6 If the prothrombin time is between 30 and 35 seconds (roughly equivalent to a prothrombin activity between 15 and 20 per cent of normal) 50 to 100 mg of dicumarol are given

7 If the prothrombin time is between 35 and 40 seconds (roughly equivalent to a prothrombin activity between 10 and 15 per cent of normal) 50 mg or less of dicumarol are given unless an extremely rapid prolongation of the prothrombin time indicates a hyper response whereupon no drug is given

8 If the prothrombin time is longer than 40 seconds indicating a prothrombin activity of less than 10 per cent of normal dicumarol is withheld on that particular day

9 More exact figures cannot be given because of the variation in response between patients and indeed in the same patient from day to day

The scheme is modified frequently according to the trend in the prothrombin clotting time on a given day The smaller doses of dicumarol given during a period in which the prothrombin clotting time is becoming longer will usually have an effect equal to that produced by larger doses of dicumarol administered while the prothrombin time is becoming shorter An occasional patient the hyporeactor may require doses of 200 mg of dicumarol almost every day to reach and maintain the desired prolongation of the prothrombin clotting time Hyperreactors encountered not uncommonly among patients with renal insufficiency severe liver damage or congestive heart failure may not require more than 50 mg a day Far better results are obtained by giving smaller doses every day than by giving massive doses on 2 or 3 days out of each week

Following the suggestion made to us by Drs Zilliacus and Jorpes we have found that the administration of a quart of milk a day to those patients whose response to dicumarol is particularly erratic helps to stabilize this response It is occasionally of

When a report is made in per cent of prothrombin activity alone there is no safeguard against laboratory errors (errors in collecting the samples of blood errors in performance of the prothrombin clotting time use of thromboplastin more or less active than usual)

The reader is referred to the *Transactions of the First Conference Blood Clotting and Allied Problems*, New York Josiah Macy Jr Foundation 1948 for a detailed and extremely illuminating discussion of the problems involved in prothrombin determinations

The Technic of Administering Dicumarol

The object in administering dicumarol is to keep the prothrombin activity of the patient s plasma between 10 and 20 per cent of normal which is equivalent in our laboratory to a prolongation of the prothrombin clotting time to between approximately 30 and 40 seconds (12 65 174 179)

The routine which we employ in administering dicumarol is as follows (42 174 179 210 213)

1 The prothrombin clotting time of the patient s whole plasma is determined before the first dose of dicumarol is given [1]

2 On the first day of dicumarol therapy if the prothrombin *time is normal or shorter than normal (hyperprothrombinemia)* 300 mg of dicumarol are administered orally in a single dose

3 Thereafter the prothrombin time is determined and reported to the clinician on each day before the dose of dicumarol is ordered for that day

4 Dicumarol is administered according to the prothrombin

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[1] If the need for the immediate administration of dicumarol is urgent if there is no evidence whatsoever of a bleeding tendency and if it is impossible to obtain a prothrombin clotting time immediately we do give an initial dose of 200 or 300 mg dicumarol without obtaining a preliminary prothrombin determination *This is then done on the following day If there is a hypo*prothrombinemia or other coagulation defect contraindicating the use of dicumarol it is still possible to stop the administration of dicumarol and to counteract the effect of the initial dose of dicumarol by the giving of blood transfusions and vitamin K The risk of this circumvention is that a rare patient with preexisting hypoprothrombinemia or coagulation defect may get into serious difficulty *within 24 hours after a single dose of dicumarol*

dilute plasma in reflecting changes in the prothrombin activity of the plasma is frequently of value in deciding upon the daily dose of dicumarol

The effect of dicumarol on the prothrombin activity of the plasma may be evident as much as a day earlier when 12 5 per cent plasma is used than when whole plasma is studied alone For practical purposes however most patients may be managed satisfactorily by the use of whole plasma studies alone

E Sterling Nichol has devised a simple formula for calculating rapidly if a patient s prothrombin time in seconds represents a satisfactory diminution of the prothrombin activity It requires that a daily control be run on whole plasma obtained from a normal subject According to this formula the plasma prothrombin clotting time on any given day is satisfactorily prolonged if it is between two and two and one half times the control reading for that day provided that the control figure is not longer than 20 seconds Thus if the control value is 15 seconds a satisfactory prolongation of the patient s prothrombin time would be between 30 and 37 seconds If the control value is 20 seconds a satisfactory prothrombin time for the patient would be between 40 and 50 seconds

Combined Heparin Dicumarol Therapy

As mentioned previously if there is an urgent need for an immediate anticoagulant effect heparin may be administered concurrently with dicumarol until the prothrombin time has been prolonged sufficiently to protect the patient completely In our laboratory this means a prolongation to 30 seconds the equivalent of a reduction in prothrombin activity to 20 per cent of normal

Heparinization may influence the prothrombin clotting time if the specimen of blood used for determining the prothrombin clotting time is taken during the first 3 hours following the injection of a dose of heparin It is customary therefore to withdraw a specimen of blood for determining the prothrombin time immediately prior to the injection of a maintenance dose of heparin usually about 4 hours after the injection of the previous dose of heparin Ordinarily the coagulation time of the whole blood is not more than 10 to 15 minutes When heparin is being

advantage to administer the daily dose of dicumarol in fractions to patients whose prothrombin response is erratic and to those rare individuals who complain of gastrointestinal upset when given large daily doses

If the prothrombin clotting time is prolonged beyond 60 seconds (prothrombin activity of less than 5 per cent) the risk of hemorrhage is very real but some patients will tolerate a considerable elevation of the prothrombin time even to 100 seconds without bleeding Hemorrhage following the administration of dicumarol depends not alone on the prolongation of the prothrombin time but on such additional factors as altered capillary fragility interruptions in vascular continuity and others which are incompletely understood If hemorrhage does occur or if the prothrombin time remains prolonged excessively 64 to 72 mg of a vitamin K preparation should be injected intravenously and repeated after 4 hours This will be discussed in greater detail in the chapter on management of hemorrhagic manifestations of dicumarol therapy

Dicumarol is administered to the majority of our patients for 20 to 30 days after the last episode of thrombosis or embolism Evidence which has confirmed the necessity for administering dicumarol for this length of time has been furnished by the study of the use of anticoagulants in the treatment of coronary occlusion with myocardial infarction In this study reported in some detail in Chapter 10 the crude mortality rate and the incidence of thromboembolic complications following coronary occlusion with myocardial infarction remained high for the first 4 weeks following the initial acute occlusion We have repeatedly observed relapses of thrombophlebitis some with serious consequences when anticoagulants have been administered for short periods of time only e g for from 6 to 10 days For many patients a short period of treatment is undoubtedly sufficient but we believe that the risk of prematurely discontinuing therapy is sufficiently great to warrant the general use of the longer term therapy

The prothrombin clotting time of the patient s plasma diluted to 12 5 per cent with saline is determined in our laboratory on each day and is reported along with the prothrombin clotting time of the whole (undiluted) plasma The greater sensitivity of the

details for the administration of the drug are essentially the same

If the patient s daily requirement for dicumarol is fairly constant he can be sent home on a specified daily dose of the drug with instructions to report twice a week for a prothrombin determination If the prothrombin level shows only minor fluctuations the interval of time between prothrombin determinations may be extended to a week When the prothrombin level fluctuates widely prothrombin determinations must be done more frequently and the dosage plan juggled about in a manner analogous to the determination of the exact insulin requirements of a difficult and labile case of diabetes mellitus It is rarely advisable to extend the interval between prothrombin determinations beyond one week

Since this method of management is somewhat hazardous it is extremely important that the patient be intelligent and cooperative and that he take the exact amount of dicumarol prescribed and appear regularly for prothrombin determinations He should be warned to report immediately to his physician any hemorrhagic manifestations or other change in his physical condition He should also be made aware of the possibility that mild trauma may produce an unusual amount of bleeding

Long term dicumarol therapy has permitted most of the patients so treated to lead fairly normal lives and to continue when necessary at a gainful occupation There have not been any serious hemorrhagic complications reported but the method requires constant vigilance on the part of the physician and faithful cooperation on the part of the patient and his family No patient should attempt to regulate his own dosage

administered in a menstruum which produces a prolonged action specimens of blood for prothrombin determinations may be obtained just prior to the administration of the heparin in menstruum each day or on every other day Dicumarol does not ordinarily prolong the coagulation time of the whole blood There is usually no difficulty in managing the administration of either drug if these points are kept in mind

Long Term Anticoagulant Therapy

In certain patients it is advisable to continue anticoagulant therapy for an indefinite period of time usually long after the patient has left the hospital and often when the patient has resumed an ambulatory status This has been accomplished successfully with small doses of dicumarol (25 mg per day) by Putnam et alii (49) in patients with multiple sclerosis and with larger doses by Nichol and Fassett (216) in an attempt to forestall coronary occlusion with myocardial infarction Wright and Foley (179 180) have reported on the successful management of long term dicumarol therapy in cases of thrombophlebitis migrans recurrent thrombophlebitis in patients with rheumatic heart disease and auricular fibrillation who periodically release showers of emboli to the peripheral circulation and following repeated coronary occlusion with myocardial infarction C E Brambel and his associates at the Mercy Hospital in Baltimore have had a very great experience with ambulatory patients maintained for long periods of time on dicumarol but they do not attempt to reduce the prothrombin activity of the patient s plasma below 40 to 50 per cent of normal a reduction which we believe is insufficient to offer the maximum protection to the patient

It is recommended that patients for whom long term anticoagulant therapy is indicated be hospitalized for a minimum of two weeks and dicumarol therapy carried out in the conventional manner The patient s response to dicumarol is thus determined and a pattern for its administration evolved The aim of long term dicumarol therapy is the same as that of the conventional course of treatment except that the prothrombin clotting time of the plasma is held between 25 and 35 seconds a reduction in prothrombin activity to between 25 and 12 5 per cent of normal The

SECTION VI

HEMORRHAGE DUE TO THE AN TICOAGULANTS AND ITS MANAGEMI NT

SECTION VI

HEMORRHAGE DUE TO THE ANTICOAGULANTS AND ITS MANAGEMENT

CHAPTER 14

The Toxicity of the Anticoagulants

HEPARIN (31 32)

ASIDE from their anticoagulant action purified preparations of heparin are completely non toxic The toxic effects encountered with the use of certain heparin preparations during the early investigations of this anticoagulant were due to impurities in the preparations Because of the ease with which heparin forms stable salts with proteins protein substances were removed with difficulty Best and his coworkers (31) found that heparin prepared from a crystalline barium salt (308) was ordinarily non toxic but that very serious reactions were encountered rarely The non toxicity of the purified commercial preparations now in use has been confirmed repeatedly

Heparin may be injected intravenously into the rabbit in single doses of as much as 500 mg and in repeated doses of as much as 10 mg per kg body weight without producing toxic reactions In a series of rabbits given 10 mg per kg body weight 4 times a day for ten days histological examination of the parenchymatous organs failed to reveal any pathological changes Purified heparin has proved to be an ideal anticoagulant in animal experiments not only because of the absence of toxic effects but because even in tremendous doses it does not produce an effect on the blood pressure or cardiac activity Both in animals and in man the microscopic examination of viscera following the administration of therapeutic doses of heparin over considerable periods of time has failed to demonstrate any pathological changes which might be ascribed to the heparin

DICUMAROL

There is no conclusive evidence that dicumarol produces toxic effects in man other than those which are secondary to its anti

coagulant action. Quick (211) and Prandoni and Wright (42, 309) stated in 1942 that there is no evidence by any available liver function test that dicumarol produces hepatic damage even when it is administered over periods of several months. We have performed an exhaustive barrage of liver function tests and have reviewed autopsy findings on patients who have been on continuous well controlled dicumarol therapy for periods of from 2 to 4 years without obtaining any evidence that long term therapy produces liver damage clinically or histopathologically. Aggeler (310) has stated that no toxic effects on the blood constituents or upon the organs or tissues have been found in man or experimental animals following dicumarol therapy.

Animal experiments indicate that dicumarol does not act directly upon organs other than the blood vascular system. They do suggest, however, that excessive dosage or prolonged administration of dicumarol produces effects on the blood vessels which may not be fully explained by the anticoagulant action alone.

Rose, Harris and Chen (311) carried out careful pharmacological and toxicity studies on dicumarol using a variety of laboratory animals and determined the median lethal doses when the drug is administered orally and intravenously. Death occurred uniformly in rabbits when dicumarol was injected intravenously in daily doses of 1 to 2 mg per kg of body weight. A majority of rabbits tolerated daily intravenous doses of dicumarol ranging from 0.1 to 0.5 mg per kg of body weight given for periods of as long as 6 weeks. Most animals dying from dicumarol developed hemorrhages into various organs and tissues and pulmonary edema. Central necrosis of the liver was observed in about one half of the rats examined and occasionally in rabbits, mice and dogs.

Wakim, Chen and Gatch (312) extended these observations and found that lethal doses of dicumarol administered intravenously to anesthetized dogs produce immediate toxic efforts and prompt terminal circulatory collapse. There was no latent period before the reaction and hypoprothrombinemia did not occur. Lethal doses of dicumarol administered intravenously to anesthetized rats produced marked splanchnic dilatation. Other effects which were observed consistently following the administration of lethal doses of dicumarol intravenously included hyperglycemia (in rabbits)

accelerated metabolic rate (in rats) and a rise in the rectal temperature (in dogs and rats)

Richard and Cortell (56) observed in post mortem studies of dogs and monkeys who had received toxic doses of dicumarol that necrosis of the liver had occurred in a number of the animals but since most of them suffered from a severe anemia the authors questioned the significance of the finding The livers of guinea pigs treated with dicumarol showed changes such as occur in vitamin C depleted animals

Roderick (313) had previously found that animals dying of the hemorrhagic sweet clover disease show no evidence of pathological changes in the liver This finding is supported by the work of Ovid Meyer and his associates and by other investigators Bingham Meyer and Pohle (39) found that the outstanding effect of lethal doses of dicumarol is hemorrhage into the tissues and organs In animals dying acutely after the administration of massive doses of dicumarol there was dilatation of the capillaries and of the small arteries and veins

McCarter Bingham and Meyer (314) extended this work and demonstrated that when massive doses of dicumarol were administered to dogs which were then sacrificed histopathological study revealed serious damage to the small blood vessels disseminated gross and microscopic hemorrhages prominent swelling of the renal glomeruli and a toxic lymphoid reaction Hepatic necrosis did not occur nor were lesions of the liver encountered consistently Bollman and Preston (41) agreed that dicumarol produces little if any damage to the liver and that when such damage is encountered it is usually secondary to local hemorrhage

More recently Irish and Jacques (315) have shown that dicumarol influences both the synthesis of prothrombin and the production of fibrinogen in experimental animals They administered dicumarol parenterally to dogs in doses of 2 5 to 20 0 mg per kg of body weight When dicumarol was injected in doses of approximately 10 mg per kg there was a significant rise in the plasma fibrinogen in from 24 to 48 hours following the injection When larger doses of dicumarol in the neighborhood of 20 mg per kg of body weight were injected into the animals the plasma fibrinogen was reduced 24 to 48 hours following injection The

dosage of dicumarol at which the response of the fibrinogen shifted from an increase to a decrease varied somewhat from animal to animal but the pattern of response was consistent In all instances irrespective of dosage the prothrombin time was prolonged and the prolongation increased with the dose of dicumarol While the changes in fibrinogen reached a peak in from 24 to 48 hours and returned to normal by the second to the fifth day following the injection the maximum prothrombin time was not reached for from 3 to 5 days after injection

Irish and Jacques conclude that these results are similar to those obtained with liver toxins and suggest that dicumarol is in fact toxic to the liver Small doses may produce mild liver damage and stimulate the production of fibrinogen Larger doses may cause more severe liver injury and depress the formation of fibrinogen It is well known that severe liver injury does depress the production of fibrinogen Schultz Nicholes and Schaeffer (316) found an immediate rise in fibrinogen after mild liver injury and these findings have been confirmed clinically and experimentally over a wide range of clinical conditions (317)

Jansen (318) has reported that while even toxic doses of dicumarol do not produce injury to the blood or kidneys in experiments on rabbits large doses of dicumarol produce pronounced fatty degeneration resembling that of chloroform poisoning *No such lesions have been demonstrated in the dog and in man with certainty*

CHAPTER 15

Hemorrhage Due to Heparin and Its Management

HEMORRHAGE is the only common complication of anticoagulant therapy—irrespective of whether heparin or dicumarol is employed Other complications are not only rare but ordinarily they are of only slight clinical significance

Bleeding that occurs during or after the administration of heparin or dicumarol is frequently unpredictable It may occur when in the case of dicumarol the prothrombin clotting time is not prolonged excessively and when in the case of heparin the coagulation time of the whole blood is within the range recommended for therapeutic effect When bleeding is encountered under these circumstances a careful search is often rewarded by the discovery of a previously unrecognized pathological condition such as malignancy or an ulceration which explains the unexpected bleeding It may occur however in patients who do not exhibit any condition predisposing to hemorrhage and in whom even the most painstaking study fails to reveal an explanation

The incidence of hemorrhagic complications following the administration of anticoagulants is significantly greater where the physician s experience with this type of therapy is limited and where the laboratory and clinical management of the therapy is less than exacting In brief except in rare instances serious hemorrhages and fatalities due to hemorrhage are a result of incompetent administration lack of proper selection of cases suitable for this treatment or of lapses in an otherwise meticulous regime

Satisfactory treatment of serious bleeding depends upon efficient emergency management of the immediate situation This includes in all instances the immediate discontinuance of the anticoagulant the administration of whole blood to replace blood loss and to combat shock the use of ancillary measures to support the patient and the administration to the patient of adequate

amounts of the specific antagonist effective against the particular anticoagulant being used

Other types of reactions have occurred rarely following the administration of heparin True anaphylactic reactions occurring immediately after injection have been reported from the Scandinavian countries but to our knowledge not in this country *They were probably due to impurities in the heparin rather than* to the drug per se Toxic reactions of a delayed nature characterized by chills fever headache and lumbar backache and occurring from 1 to 2 hours after the injection of heparin are apparently due to impurities in the preparation since they have rarely been encountered since the introduction of purer and more potent commercial preparations

Of greater practical significance are local reactions inherent to the parenteral route of administration These occur not infrequently and may be of considerable significance Despite the anticoagulant action of heparin its administration intravenously has been followed by venous thrombosis at the site of injection This is probably due to severe trauma to the vein and to its supporting tissues As mentioned previously the injection of heparin in Pitkin s menstruum is commonly accompanied by such severe pain that the patient may refuse to continue these injections

The injection of heparin subcutaneously or intramuscularly has been followed occasionally by local inflammatory reactions which have rarely resulted in abscess formation These complications are common to many forms of parenteral therapy and must in general be attributed to the technic of administration

The incidence of serious hemorrhage following the use of heparin is low It is however not uncommon for bleeding to occur in and around operative wounds in instances where heparin is administered postoperatively Since heparin has been used widely in the management of postoperative thromboembolism the number of instances in which hematomata have occurred is considerable and has perhaps given the impression that bleeding from heparin is to be feared Bleeding because of heparin is extremely uncommon when the continuity of the vascular walls is intact (Cf pages 110 113)

Some fatalities have occurred from cerebral hemorrhage when

heparin has been administered without adequate control Transient hematuria has been reported rarely during heparin therapy but has not proceeded to serious consequences even when the drug has been continued Hemorrhage into the pleural cavity of patients who have suffered a pulmonary embolism and to whom heparin has been administered has likewise been reported in isolated instances Jorpes (32) in commenting upon this complication points out that the hazard of progressive or recurrent embolization is far greater than is that of serious bleeding following the use of heparin

The first step in controlling a significant amount of bleeding due to or aggravated by heparin is to withdraw the drug Transfusions preferably of whole fresh blood may be given to restore blood loss and to stimulate the process of blood coagulation Citrated blood may be used but it should be fresh

Protamine and Toluidine Blue

There are two substances which possess what is apparently a specific antagonistic action to the anticoagulant effect of heparin These are the azo dye toluidine blue (319) and the protein from fish roe protamine sulfate (320) Either of these substances may be administered intravenously in doses of from 1 to 4 mg per kg of body weight Both act promptly in restoring the coagulation time of whole blood to normal but their effect may be transient and repeated injections on subsequent days may be necessary It is obviously advisable to determine the clotting time of the whole blood at frequent intervals until it has become normal and remained so for a period of several days

Toluidine blue or protamine sulfate are fairly well tolerated when administered intravenously in man (321) A dose of about 2 mg per kg of body weight appears to be adequate with either drug They have been ordinarily administered intravenously over a two hour period in from 250 to 500 cc of normal saline

The toxicity of toluidine blue (321) is relatively unknown It is strongly hemolytic in normal dogs but hemolytic reactions have not been encountered when therapeutic doses have been administered to man Both the urine and the stool become highly colored and remain so for 36 to 48 hours following the administra

tion of therapeutic doses but the skin of the patient does not become discolored when such doses are used Neither toluidine blue nor protamine sulfate is effective when administered orally

The protamines neutralize heparin in vivo and in vitro although they themselves possess anticoagulant properties (322 324) Because protamine sulphate is a foreign protein and because in early animal experiments its intravenous injection into the dog was followed by serious toxic effects it has been feared that protamine could not be administered intravenously into man without a considerable hazard (319) Apparently however the reactions incited in the dog are anaphylactoid reactions peculiar to the canine species since they do not occur in other experimental animals The untoward reactions anticipated in man have not occurred in the somewhat limited clinical experience so far accumulated (32 325 326) The experience with toluidine blue is even more limited than that with protamine (316) and both substances should be used with caution at the present time

CHAPTER 16

Hemorrhage Due to Dicumarol and Its Management

MILD gastrointestinal disturbances are reported rarely following the administration of dicumarol Ordinarily nausea and dyspepsia alone occur but vomiting and abdominal pain have been reported occasionally Several observers have reported that when the daily amount of dicumarol is given in divided doses these gastrointestinal complaints subside It is difficult to believe that they are the result of any specific action of dicumarol

Skin rashes of various types most usually erythematous have been reported infrequently during the course of dicumarol therapy but in most instances the patients have been receiving other drugs at the same time and it is impossible to state with certainty that dicumarol was an etiological factor

It has been our practice to continue the administration of dicumarol in these circumstances and the gastrointestinal or skin manifestations have invariably cleared spontaneously We have not seen any proven allergic reactions to dicumarol but E V Allen has mentioned the unusual occurrence of urticaria during dicumarol therapy (65)

Hemorrhages complicating dicumarol therapy have been reported in considerable numbers not infrequently of serious consequence and occasionally fatal in outcome This is not surprising since tablets of dicumarol can be dispensed so easily that the drug is sometimes used under circumstances in which the necessarily exacting laboratory control is either not available or is not utilized fully It is impossible to discuss in detail the numerous instances in which lapses in proper management have resulted in unfortunate and sometimes tragic consequences

In our experience it has been uncommon that a serious hemorrhage due to dicumarol has not been the direct result of unreliable laboratory reports improper management of therapy or the

failure to carefully observe the patient and his prothrombin clotting time[1] One is reminded constantly of the plea by Karl Paul Link to ask that human subjects be shown at least as much consideration as we give our standardized assay animals We never administer the anticoagulant without determining the prothrombin level (or activity) It is my duty to indicate at this late date nearly 3 years after the drug has become available for clinical research some clinicians still feed it to human subjects without following either the whole blood coagulation time or the prothrombin time But I must confess that when I learn that a clinician has induced a frank case of the hemorrhagic sweet clover disease of cattle in man my usual buoyant spirits are bruised I regard such blundering as a direct assault on the integrity of our work as recorded in the *Journal of Biological Chemistry* There is not only a tremendous spread between the detectable and the lethal dose of this anticoagulant—there is also a wide margin between the detectable dose and the dosage that can cause hemorrhage (37)

Incidence of Hemorrhage

In 1946 Aggeler (310) collected and tabulated the incidence of hemorrhagic complications following dicumarol therapy from 9 clinical reports in the American literature (270 309 327 333) In a total number of 1 471 patients treated with dicumarol hemorrhagic complications had occurred in 123 patients (8 3 per cent) In certain of these reports such minor bleeding as microscopic hematuria mild epistaxis and minor bleeding from wounds was included The deaths of 5 patients (0 34 per cent of those treated) were attributed to dicumarol therapy

It is of interest that in this collected series by far the highest incidence of hemorrhage was reported by Prandoni and Wright (309) an incidence of 40 per cent but without deaths These cases were studied in 1940 when the optimum dosage of dicumarol was as yet not known and when the technic available for performing the prothrombin clotting time was crude Furthermore the

[1] Having had the experience of reviewing many published and unpublished reports of cases presenting hemorrhagic complications we feel justified in making this conclusion most emphatically

patients reported in this series were mostly malnourished the importance of which was not fully appreciated until several years later This incidence has been reduced to less than 10 per cent during subsequent experience

Examples of the Scandinavian experience are the reports by Lehmann (334) and by Bruzelius (272) Lehmann treated 100 cases of venous thrombosis (phlebothrombosis) and 32 cases of thrombophlebitis with dicumarol Hemorrhage of any degree occurred in about 1 case out of every 10 cases treated but was profuse in only 1 case out of every 100 It was controlled readily by the use of vitamin K and blood transfusions and no deaths ensued Bruzelius reported that hemorrhages had occurred in 64 cases (4 4 per cent) of 1 448 patients treated with dicumarol post operatively In the total series of 1 656 patients treated with dicumarol and reported by Bruzelius profuse hemorrhage oc curred in 13 patients and death could be attributed to dicumarol therapy in 2 or perhaps 3 instances

The periodic reports of the cumulative experience with dicu marol at the Mayo Clinic are of considerable interest since they represent not only a very large experience with the drug but one which has been acquired with the most careful management of therapy

In 1945 Barker Cromer Hurn and Waugh (331) reported on 1 000 surgical patients given dicumarol postoperatively Minor bleeding has been encountered in 39 patients (3 9 per cent) major bleeding in 25 patients (2 5 per cent) a total of 64 patients (6 4 per cent) of those treated There was a single death attributed to dicumarol

In July 1946 Allen (164) reported on 1 686 surgical patients treated postoperatively with dicumarol Minor hemorrhages had occurred in 3 1 per cent and major hemorrhages in 1 9 per cent of these cases Two deaths occurred from hemorrhage but in 1 case bleeding was obviously not caused by Dicumarol and there was doubt that the drug was responsible for bleeding in the other case

In May 1947 Allen Hines Kvale and Barker (335) reported

This was due to hemorrhage from a carcinoma in the gastrointestinal tract —I S W

on 2,307 patients treated with dicumarol, 2,019 of these postoperatively and 288 during the course of medical illnesses. Among the 1,983 patients treated postoperatively, minor bleeding had occurred in 3.4 per cent and serious bleeding in 1.8 per cent. The 2 deaths mentioned in this report are those referred to in previous reports from the Clinic and there had been no subsequent deaths. Among the 288 patients with medical conditions to whom dicumarol had been given, 2 patients (0.66 per cent) suffered minor bleeding and 3 patients (1.0 per cent) major bleeding. Major bleeding occurred from the gastrointestinal tract in 2 instances and subcutaneously in 1 instance.

The experience of the American Heart Association's Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Occlusion with Myocardial Infarction is discussed in Chapter 10. In brief, 7 hemorrhagic manifestations believed to be due to or aggravated by anticoagulants were observed in every 100 cases treated. In 432 patients treated with anticoagulants, 30 hemorrhages were observed clinically and one half of these were mild in severity. Only 1 instance of bleeding could be classified as severe. It should be noted that hemorrhages occurred in 6 per cent of patients not receiving anticoagulants.

Instances of Hemorrhage

Although statistics on the incidence and outcome of bleeding following the administration of dicumarol are of great value in assessing the importance of the hemorrhages due to the drug, they are perhaps of less interest to the practicing physician than are the details of the more dramatic instances of severe and even fatal hemorrhage. Conversations with practising physicians suggest that the majority of untoward reactions to dicumarol are not reported in the literature. Those cases of severe and even fatal hemorrhage which have been reported indicate that bleeding may occur under a wide range of circumstances, may involve any one or more of the body tracts or systems and may be influenced by factors other than the hypoprothrombinemia produced by dicumarol.

Where bleeding occurs from a single tract of the body during dicumarol therapy, it is imperative to consider that local cause for or source of bleeding may exist before attributing it solely

to the effect of the anticoagulant In the presence of ulcerations or wounds of the skin or mucous membranes bleeding is apt to occur when the prothrombin time is only moderately prolonged to therapeutic levels or even less In cases which have bled prior to the institution of anticoagulant therapy this bleeding is apt to

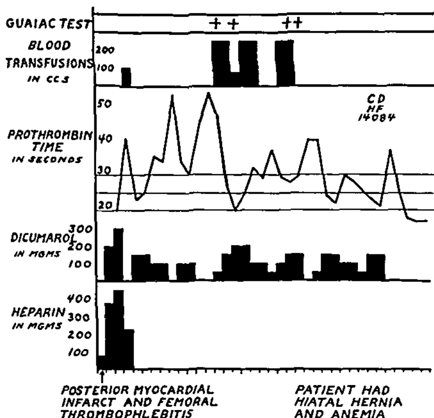


FIGURE 16 Bleeding at moderate prolongations of the prothrombin clotting time in patient with hiatal hernia from which there had been previous bleeding sufficient to produce anemia

be aggravated under dicumarol In others bleeding may occur for the first time when dicumarol is administered We have encountered such bleeding in the presence of cancer peptic ulcer hiatal hernia hemorrhoids and of course postoperatively after surgery on the gastrointestinal tract

The patient whose course is represented graphically in Figure

16 had a hiatal hernia confirmed radiologically which bled sufficiently during the administration of dicumarol to produce tarry stools although the prothrombin clotting time did not exceed 52 seconds That the bleeding was not due solely to dicumarol is suggested by the fact that this patient had bled sufficiently prior to anticoagulant therapy to develop a significant anemia

In most reported instances of severe bleeding from the gastro intestinal tract there has been a gastric ulcer or some other in trinsic disease or the history of a recent surgical operation on the gastrointestinal tract It is of course difficult to say in such instances that bleeding would not have occurred if dicumarol had not been administered Abramson (336) reported serious bleeding from a gastric ulcer in a woman of 47 following the administration of 2 250 mg of dicumarol in nine days Fahraeus (337) reported a death from gastric bleeding after dicumarol had been given in doses of 250 mg daily for 10 days *In neither case were prothrom bin clotting times performed during the course of therapy* Cheney s case (269) described briefly in Chapter 11 first mani fested severe gastrointestinal bleeding 11 days after a gastric re section and 4 days after the institution of dicumarol therapy It is not made clear in the report of this case why this patient might not have bled from the operative site if dicumarol had not been administered Fahraeus (337) has also reported severe post partum hemorrhage in a woman who had received 6 500 mg of dicumarol over a period of 18 days for suspected postpartum thrombosis This represents an average daily dose of 360 mg for the entire period an excessive and dangerous dose regardless of laboratory findings

It has been observed repeatedly that hematuria is the most common type of bleeding encountered during the administration of dicumarol In most instances this is microscopic only not more than from half a dozen to a dozen erythrocytes being seen per high power field in the urinary sediment The microscopic hema turia usually disappears or remains insignificant even though the administration of dicumarol is continued In only an occasional case is the hematuria aggravated by continued anticoagulant therapy

Rosenbloom and Crane (338) have reported a case of massive

hematuria in a 32 year old male beginning 2 days after the completion of a course of therapy consisting of 2 300 mg of dicumarol in seven days an average of almost 330 mg a day for a week Bleeding ceased after repeated transfusions Hendrick (339) has observed massive hematuria in several cases post operatively Levan (340) reported that 1 of 66 cases treated with ordinary doses of dicumarol showed gross hematuria

Where bleeding is generalized or where it involves more than one tract of the body it may be attributed more readily to the influence of dicumarol Cahan (341) described an instance of hemorrhage and purpura developing in a patient who had re ceived 2 800 mg of dicumarol over a period of 32 days The bleeding time was prolonged during the height of the hypo prothrombinemia and the patient improved as both the bleeding time and the prothrombin clotting time returned to normal

Although hemorrhagic complications to dicumarol therapy are observed with prothrombin times at all levels bleeding is more apt to be encountered when the prothrombin time is excessively prolonged In our experience hemorrhagic manifestations are much more common when the prothrombin time is prolonged to 60 or 70 seconds or longer and particularly when the prothrom bin time is maintained at such excessive levels It is true that many patients will tolerate such prolongation of the prothrombin time even when it is sustained for some days but it is unwise to permit such levels to exist unnecessarily Not only is the hazard of bleeding increased but in animals if the exaggerated pro thrombin times are sustained there is damage to the walls of the vessels and hepatic necrosis may result from hemorrhage into the liver parenchyma (39 156 311 314 315) Although such patho logical changes have not been described for man a conservative attitude is certainly advisable

Figure 17 gives the essential facts in a case in which a shower of erythrocytes appeared in the urine when the prothrombin clotting time reached and was maintained at levels between 70 and 90 seconds No effort was made to reduce the prothrombin clotting time by means other than withholding dicumarol After 1 week the prothrombin clotting time fell and the hematuria cleared spontaneously without further attention

In the presence of hepatic disease (including hepatic congestion secondary to congestive heart failure) and of renal disease when the patient's response to dicumarol may be exaggerated and the prothrombin times obtained in response to ordinary doses of dicumarol may fluctuate widely bleeding is apt to occur The

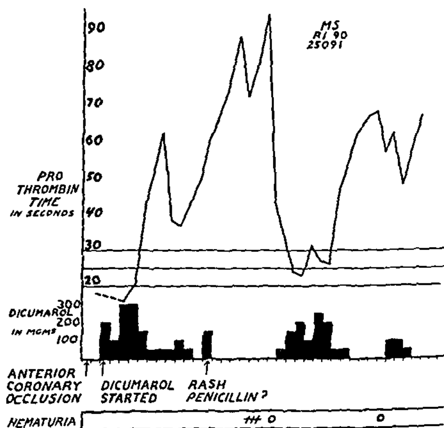


FIGURE 17 Transient hematuria occurring upon excessive prolongation of prothrombin clotting time Withholding of dicumarol followed promptly by a fall in the prothrombin time and clearing of the urine

patient represented by Figure 18 had a grossly enlarged liver and although a barrage of hepatic function tests gave normal results the response to relatively small amounts of dicumarol was exaggerated The prothrombin clotting time remained between 60 and 100 seconds for a week during which a shower of erythrocytes appeared in the urine When dicumarol was withheld the pro

thrombin clotting time fell and the urine cleared spontaneously

In other instances when the hepatic or renal dysfunction is reversible and is relieved as for example the relief of passive congestion of the liver secondary to congestive heart failure or the improvement in renal function after a transient uremia the tendency is for the patient to require smaller doses of dicumarol

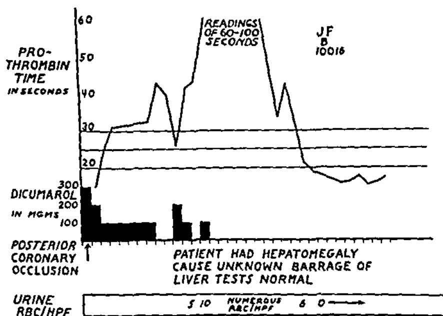


FIGURE 18 Excessively prolonged prothrombin clotting time following relatively moderate doses of dicumarol in a patient with hepatomegaly Prothrombin time fell and hematuria cleared about one week after dicumarol was withheld

and to respond in a more regular manner to a given dose thus simplifying the matter of administration and decreasing the chances of bleeding

The risk of bleeding when dicumarol is taken indiscriminately is illustrated by the case reported by Draper (342) In this instance a graduate nurse age 16 took 8 or 10 tablets of dicumarol for her arthritis Approximately one week later she developed gross hematuria grossly bloody stools extensive subcutaneous ecchymoses on her trunk and limbs and bleeding from her gums There

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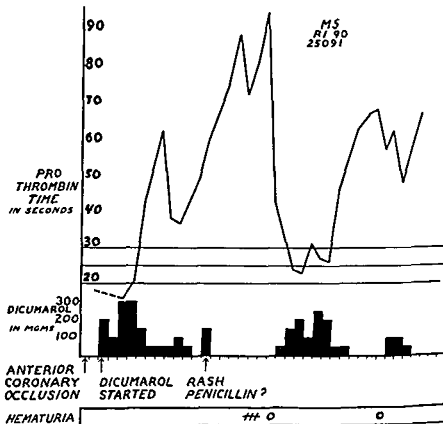


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from the gums was noted but two days later hematuria appeared Two days later the patient was admitted to the hospital with bleeding gums ecchymoses over the extremities and hematuria Her prothrombin clotting time was prolonged to from 60 seconds to more than 6 minutes during the period of observation and the coagulation time of her whole blood ranged between 9 and more than 49 minutes Repeated transfusions of citrated blood were ineffectual in controlling the bleeding or in restoring the prothrombin activity to normal *Vitamin K was not given*

At autopsy hemorrhages were described in the skin the meninges the retroperitoneal tissues the renal pelves the urinary bladder the stomach and the duodenum It is of interest that ancillary anatomic diagnoses included not only advanced generalized arteriosclerosis but cirrhosis of the liver as well The main feature of the autopsy findings was the marked engorgement of all the blood vessels except the larger trunks This engorgement was most pronounced in the capillaries the arterioles and the venules Hemorrhagic lesions were not associated with any apparent defect in the continuity of the vessel walls but resembled those seen in essential thrombocytopenic purpura

The Treatment of Hemorrhage and of Excessive Hypoprothrombinemia Due to Dicumarol Therapy

The Use of Blood Transfusions

When it is desirable to reduce an excessively prolonged prothrombin time or to staunch bleeding which occurs as a result of hypoprothrombinemia the transfusion of 500 cc of fresh whole blood (may be citrated) is usually effective temporarily Banked blood which has been stored for more than 24 hours is usually less effective than fresh blood Since the prothrombin time tends to increase again in from 2 to 6 hours after a transfusion of fresh blood it is usually necessary to give repeated transfusions over a period of several days in order to control bleeding or to restore the prothrombin level of the blood to normal The effect of transfused whole blood appears to be due simply to the addition of the prothrombin in the donor s blood to the patient s prothrombin deficient plasma It may serve to sustain the patient s plasma prothrombin activity until the effect of dicumarol has worn off

was severe low back pain due perhaps to bleeding into the renal pelves or retroperitoneally Physical examination revealed multiple ecchymoses and scattered petechiae on her skin and mucous membranes There was a depression of the plasma prothrombin activity to less than 10 per cent of normal and the coagulation time of the whole blood was prolonged The patient recovered uneventfully although it is not clear that a blood transfusion and repeated injections of vitamin K hastened the recovery The prothrombin clotting time did not return to normal until the 6th hospital day

Thorson (343) has reported an interesting case of dicumarol poisoning in a woman who had taken *14 grams of dicumarol in 3 weeks* There was severe hemorrhage from the mucous membranes and into the peritoneal cavity but no evidence of renal or hepatic damage Despite repeated blood transfusions and the administration of vitamin K orally in amounts of 200 to 400 mg daily supplemented by small doses of vitamin K intravenously (10 to 30 mg daily) bleeding did not cease for 18 days Three and one half months later without having taken any more dicumarol the patient developed further bleeding from the nose the gums and the vagina and both cutaneous and subcutaneous hemorrhages During the first week of treatment of this relapse only blood transfusions were given The bleeding continued and the prothrombin activity did not rise above 30 per cent rising to that level after each transfusion and then falling back rapidly to about 10 per cent After a week vitamin K was given intravenously in doses of 50 mg twice daily but the transfusions were continued for 4 days The prothrombin clotting time did not return completely to normal for a full week after parenteral vitamin K therapy had been started Bleeding ceased however shortly after the institution of vitamin K therapy

Shlevin and Lederer (344) have reported in detail the history and post mortem findings in *a patient who died of uncontrollable hemorrhage following dicumarol therapy* The patient was a 79 year old woman who had been treated with 100 mg of dicumarol a day for 21 days because of a thrombosis of the right retinal vein *No prothrombin clotting times were run while dicumarol was being administered* Dicumarol was discontinued when bleeding

nones with a single long side chain Both are fat soluble and depend for their absorption from the gastrointestinal tract upon the presence of bile salts Vitamin K_1 has the chemical formula 2 methyl 3 phytyl 1 4 naphthoquinone and is obtained synthetically or from natural sources especially alfalfa Vitamin K which has about 60 per cent of the antihemorrhagic activity of vitamin K_1 probably has the chemical formula 2 3 difarnesyl 1 4 napthoquinone It was obtained first from putrefied fish meal A considerable number of compounds have been synthetized and tested for vitamin K activity Most of those which possess such activity are basically 1 4 naphthoquinones or the corresponding hydroquinones A few however are not

Phthiocol (2 methyl 3 hydroxy 1 4 naphtholquinone) was the first preparation shown to possess not only physical and chemical properties similar to those of vitamin K but also its marked antihemorrhagic activity Of the compounds studied subsequently 2 methyl 1 4 naphthoquinone has the most potent antihemorrhagic activity However whereas vitamin K appears to be completely non toxic in even large doses 2 methyl 1 4 naththoquinone may exhibit toxic properties in large doses

The preparations possessing vitamin K activity which are commercially available for therapeutic use are chiefly vitamin K_1 for oral administration (with the addition of bile salts) in emulsions for intravenous administration or in oils for intramuscular injection 2 methyl 1 4 naphthoquinone (menadione) for oral or intravenous use and the water soluble derivatives 4 amino 2 methyl 1 naphthol hydrochloride (synkamin) and 2 methyl 1 4 naphthohydroquinone 3 sodium sulfonate (hykinone) which may be given orally without the addition of bile salts or intravenously Vitamin K and the simpler naphthoquinones become effective at about the same rate following administration but the former appears to have a somewhat more prolonged action The water soluble derivatives of 2 methyl 1 4 naphthoquinone are less active than the parent but they are effective clinically The natural and synthetic naphthoquinones used more commonly for their vitamin K activity are listed in Table XI

Although the dosage of these preparations with vitamin K activity varies somewhat with the potency of the preparation and the indication for its administration doses in the range of 1 to 5

and the synthesis of prothrombin has been resumed in the liver

A patient seen recently in consultation by one of us (I S W) received 12 transfusions of bank blood for massive bleeding due to dicumarol without any apparent effect on either the prothrombin level or upon the bleeding Two 500 cc transfusions with fresh whole blood (citrated) brought the prothrombin time to normal and stopped the bleeding within a few hours

The Use of Lyophilized Plasma

Lyophilized plasma reconstituted with 0 1 per cent citric acid and distilled water has been shown by Strumia (345) to possess a normal prothrombin content comparable to that of fresh whole blood It has the advantage over whole blood of not being diluted to approximately 50 per cent with cellular elements

Cosgriff Cross and Habif (346) confirmed Strumia s finding by determining the prothrombin activity of random samples of lyophilized plasma The prothrombin of these samples averaged between 75 and 100 per cent of normal They administered lyophilized plasma in amounts of 500 cc to 13 patients who had developed an excessive hypoprothrombinemia during dicumarol therapy In no instance was there significant hemorrhage at the time of transfusion Lyophilized plasma proved to be effective in reducing the prothrombin time immediately to within a safe range There was however a subsequent prolongation of the prothrombin time similar to that seen following the transfusion of whole blood and occurring as early as 6 hours after the administration of lyophilized plasma

These authors warn that while lyophilized plasma may serve to maintain the prothrombin time within a safe range temporarily and until more permanent restoration of normal prothrombin activity is obtained by the use of vitamin K or through the spontaneous reactivation of prothrombin synthesis pooled lyophilized plasma should be used only when grouped fresh blood is not available because of the risk of transmitting homologous serum hepatitis

The Use of Vitamin K Preparations

Vitamin K (239 244) exists naturally in at least 2 forms vitamin K_1 and vitamin K_2 both of which are substituted naphthoqui

mg daily are sufficient for certain purposes Doses in this range have been recommended for the simple vitamin K deficiencies which may exist in obstructive jaundice in severe hepatic damage in intestinal diseases and in hemorrhagic disease of the newborn (245 259 256 258) Larger doses are probably more effective

It has been long known among investigators however that doses of this magnitude are completely ineffective in correcting the excessive hypoprothrombinemia or bleeding which results occasionally from the administration of dicumarol Apparently this fact is not generally recognized by clinicians since reports still appear in the literature in which picayune doses of vitamin K preparations are given to antagonize the anticoagulant effect of dicumarol

It has been demonstrated repeatedly and in a variety of species including man that when the synthetic naphthoquinones are administered either orally or parenterally in the doses employed successfully *in the treatment of ordinary vitamin K deficiency* they do not usually either diminish the degree or shorten the duration of the hypoprothrombinemia resulting from the administration of dicumarol (266 297 317 319) On the other hand it is well established both experimentally and clinically that when preparations possessing vitamin K activity are administered in large doses they will usually counteract the hypoprothrombinemia and control the bleeding due to dicumarol

This fact has been demonstrated in a variety of laboratory animals (266 317) and has been confirmed clinically in man by many observers (39 148 350 354) For example Shapiro Redish and Campbell (350) found that large doses of menadione (2 methyl 1 4 *naphthoquinone) given orally or intramuscularly to* man prevented the prolongation of the prothrombin time following the administration of dicumarol

Cromer and Barker (355) administered menadione bisulfite intravenously usually in a single dose of 64 mg to 37 patients who had an excessively prolonged prothrombin time following the administration of dicumarol In all but 2 patients the prothrombin time was shortened only slightly in 3 cases but to a marked degree and in a relatively short time in 32 patients Bleeding which had occurred in 3 cases following the use of dicumarol

TABLE XI

NATURAL AND SYNTHETIC NAPHTHOQUINONES USEFUL THERAPEUTICALLY FOR THEIR VITAMIN K ACTIVITY

	Chemical Name	Solubility	Route of Administration
	Naturally Occurring Naphthoquinones		
Vitamin K_1	2 methyl 3 phytyl 1 4-naphthoquinone	Fat soluble	Orally Intramuscularly in oil Intravenously in emulsions
Vitamin K_2	2 3-difarnesyl 1 4-naphthoquinone	Fat soluble	
	Synthetic Naphthoquinones*		
Phthiocol	2 methyl 3 hydroxy 1 4-naphthoquinone	Water soluble sodium salt	Intravenously
Menadione	2 methyl 1 4 naphthoquinone	Fat soluble	Orally in vegetable oil Intramuscularly in oil Intravenously
Synkamin	4 amino-2 methyl 1 naphthol hydrochloride	Water soluble	Orally Subcutaneously Intramuscularly Intravenously
Hykinone	2 methyl 1 4-naphtho hydroquinone 3 sodium sulphonate	Water soluble	Intravenously
Synkavite	2 methyl 1 4 naphtho-hydroquinone diphosphoric acid ester	Water soluble	Intravenously

* There are many other synthetic naphthoquinones with some degree of vitamin K activity

mg daily are sufficient for certain purposes Doses in this range have been recommended for the simple vitamin K deficiencies which may exist in obstructive jaundice in severe hepatic damage in intestinal diseases and in hemorrhagic disease of the newborn (215 252 256 258) Larger doses are probably more effective

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ceased in 2 patients after menadione had been given and with the 3rd patient after menadione and a blood transfusion

Davidson and MacDonald (351) were able to restore to normal prolonged prothrombin times induced by dicumarol in 3 out of 4 cases given large doses of a preparation containing vitamin K_1 oxide intravenously Lehmann (334) reported that hemorrhage following the administration of dicumarol was controlled by the use of blood transfusion and large doses of methyl naphthoquinone dihydrosulfate given orally

The minimum dose of the synthetic vitamin K preparations necessary to exhibit this effect consistantly is in the range of 64 to 75 mg depending upon the preparation used The route of administration must be intravenous to assure prompt action The patient s condition and his prothrombin clotting time must be checked at frequent intervals and additional doses of similar magnitude administered at 4 hour intervals until the response is satisfactory Repeated doses and even single doses of the vitamin K preparations totalling from 500 to 1 000 mg have been given clinically without apparent ill effect

When the prothrombin clotting time of patients receiving dicumarol becomes excessively prolonged (when the prothrombin activity is reduced to 10 per cent or less of normal) 30 to 60 mg of menadione bisulfite may be given intravenously and subsequent doses of dicumarol omitted or reduced in amount If bleeding of a significant degree occurs 60 72 mg of menadione bisulfite may be given intravenously and followed immediately by a transfusion of 500 cc whole fresh blood The vitamin K preparation should be repeated at regular intervals of 4 hours until the prothrombin clotting time has returned to and been maintained at approximately normal Transfusions may be given periodically to control the bleeding and to combat any anemia which develops

Vitamin K_1 Oxide

In certain instances patients who fail to respond satisfactorily to the administration of the synthetic vitamin K preparations administered in even massive doses will respond to large doses of vitamin K_1 oxide given intravenously We have seen this in 2 patients with hypoprothrombinemia and a hemorrhagic diathesis

secondary to a blood dyscrasia of unknown etiology When the synthetic naphthoquinones and multiple transfusions failed to correct the hypoprothrombinemia or reduce the bleeding vitamin K_1 oxide in doses of 1 000 mg reduced the prothrombin time to normal Furthermore as tested by the two stage method the prothrombin level which was zero after repeated transfusion and the administration of synthetic vitamin K rose rapidly after the administration of vitamin K_1 oxide

Davidson Freed and MacDonald (356) gave vitamin K_1 oxide intravenously in an alcohol water emulsion prepared by a modification (351) of the method of Seligman (357) to 10 patients on dicumarol whose prothrombin clotting times were prolonged excessively (from 60 to 170 seconds) and whose coagulation times were also prolonged to from 14 to 20 minutes One half to 3 grams of vitamin K_1 oxide were administered intravenously over a period of from 1 to 2½ hours These large doses of vitamin K_1 oxide reversed both the hypoprothrombinemia and the prolonged coagulation time in all 10 patients The effect was achieved even when the administration of dicumarol was continued after the giving of the vitamin K_1 oxide However coagulation times did not become normal for from 3 5 to 36 hours

Lucia and Aggeler (353) found that the hypoprothrombinemia induced in a human subject by the administration of dicumarol was corrected by the intravenous administration of a single massive dose of vitamin K_1 oxide However they noted that the period of time which elapsed between the administration of the vitamin K and the cessation of hemorrhage was too long for control of massive bleeding clinically

Late Pregnancy

In Chapter 11 the risk of administering dicumarol to women late in pregnancy was discussed It was pointed out that not only may the mother bleed profusely at the time of delivery but that the infant may hemorrhage during or following birth It is suggested that when dicumarol is being administered to a pregnant woman at term it be withheld from the time the patient goes into labor With the onset of labor the patient should be given a vitamin K preparation intravenously in sufficiently large doses and re

peated as often as indicated by the patient s prothrombin clotting time Immediately after delivery and periodically through the first week of life the infant should be given vitamin K parenterally Following delivery the mother may again be placed on dicumarol if necessary The infant should be weaned or at least not be allowed to nurse at the breast until dicumarol has been dis continued and the mother s plasma prothrombin activity restored to normal

Miscellaneous Observations on Vitamin K

Smith Warner and Brinkhous (253) Pohle and Stewart (358) Seligman et al (357) and Shapiro and Richards (359 360) have reported instances in both experimental animals and man in which the administration of synthetic vitamin K to subjects whose prothrombin clotting times were already prolonged as a result of liver damage has resulted in a transient further prolongation of the prothrombin time This has occurred following both oral and parenteral administration Shapiro and Richards (359 360) have also observed in dogs whose livers have been damaged by carbon tetrachloride and in human subjects with liver damage that the administration of synthetic vitamin K may cause a transient pro longation of a previously normal prothrombin clotting time The reason for this type of reaction is not clear

Unger and Shapiro (259) suggest however that when vitamin K is administered to patients with prolonged prothrombin clot ting times particularly in the presence of liver damage small initial doses be used If the prothrombin clotting time fails to respond or if it is actually prolonged by the administration of vitamin K prothrombin activity can be augmented by the trans fusion of fresh whole blood or possibly of frozen plasma (253)

Unger and Shapiro (361) have shown that the injection of large amounts of vitamin K may accelerate the production of prothrom bin in some normal subjects so that a temporary hyperprothrom binemia occurs The demonstration of hyperprothrombinemia ordinarily requires that the prothrombin clotting time be de termined on 12 5 per cent diluted plasma since the determination using whole plasma is not sufficiently sensitive to demonstrate

consistently the changes of slight magnitude which are involved (299)

Richards and Shapiro (359) have shown that the toxicity of menadione bisulfite is due to the quinone radical which produces its effect acutely and irrespective of prothrombin synthesis Repeated injections of menadione into dogs in doses of 100 to 150 mg per kg of body weight are lethal while slightly lower sublethal doses produce a depression of the erythrocytes and hemoglobin content of the blood These revert promptly to normal when the drug is withdrawn Doses of this magnitude are of course far in excess of those used in man When doses of menadione bisulfite approximately 10 times as great as those usually employed were given to man every day for a week significant changes in the blood could not be demonstrated

Most of the reports dealing with the effect of vitamin K on the hypoprothrombinemia induced by the administration of dicumarol have utilized the one stage method (89) or one of its modifications for the determination of the prothrombin clotting time Boyd and Warner (362) using the two stage method (97) report that menadione given orally in doses of 50 mg per day or menadione bisulfite (Hykinone) given intraperitoneally in doses of 1 0 cc per day have no detectable influence on the hypoprothrombinemia produced in rats by the use of dicumarol The results were consistent whether the menadione or its sulfite were given before during or after the administration of dicumarol

Impressed by the role of subintimal hemorrhage in the formation of arterial thrombi particularly those in the coronary vessels (363 364) and by the possible role of hypoprothrombinemia in the production of such intimal hemorrhages Doles (365 369) has advocated the administration of large doses of vitamin K to patients immediately following a coronary thrombosis and to patients in whom an acute coronary occlusion may be anticipated This work has not been confirmed as far as we know There is no published evidence as far as we are aware that such patients suffer a hypoprothrombinemia and in fact the work of Shapiro (299) and others suggests that thromboembolism may be associated with a hyperprothrombinemia It is not clear whether such hyper

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SECTION VII

FAILURES AND ABUSES OF ANTICOAGULANT THERAPY

prothrombinema precedes or whether it accompanies the thromboembolic incident On the basis of present evidence we cannot subscribe to Doles hypothesis and we advise against the use of vitamin K as a measure to be employed in the treatment of coronary thrombosis with myocardial infarction

CHAPTER 17

Failures with Anticoagulant Therapy

IT IS unreasonable at the present time to expect that the administration of the anticoagulants will prevent the occurrence of thromboembolic phenomena in every instance Not only is our understanding of the action of the anticoagulants incomplete but so also is our comprehension of the various factors which influence the formation of intravascular clots In dealing with thromboembolic phenomena we encounter a variety of complex processes of which the coagulation of the blood is but one albeit an important one Although certain factors involved in thrombosis are known and understood it is not yet possible to evaluate the relative importance of each individual factor in a given thromboembolic episode

It is usually impossible to be certain at what moment a thromboembolic process begins In the instance of an embolus we realize that a thrombus already exists from which the embolus has arisen It appears probable that the genesis of a thrombus precedes by hours perhaps sometimes by days the clinical manifestations of the condition For example in phlebothrombosis where there is initially no significant inflammatory reaction symptoms and signs do not appear until the thrombotic process has completely occluded the veins or has at least interfered seriously with the local circulation through them We are dealing with phenomena which may be manifested only indirectly by their interference with the circulation to or from a given organ or area of the body

There is at present no test nor barrage of tests by which we can anticipate with certainty the onset of a thromboembolic incident Until it is possible to predict with considerable accuracy in which cases and under what circumstances such incidents will occur we can assess the value of anticoagulant therapy only by determining statistically to what degree such therapy will reduce

binemia as a point in the differential diagnosis between posterior myocardial infarction and pulmonary infarction In our experience hyperprothrombinemia has occurred though not consistently in instances of all types of thromboembolic disease We have seen several families in which this tendency occurs in many members

Heparin Tolerance

There are two laboratory procedures by which an apparent hypercoagulability of the blood may be demonstrated in certain groups of patients irrespective of whether they have suffered a thromboembolic episode De Takats (373 375) has devised a simple in vivo test of the clotting mechanism in which a small amount of heparin is injected intravenously and coagulation times determined at 10 minute intervals for 40 minutes He has found a group of heparin resistant persons including patients in the early postoperative period following cardiovascular accidents such as coronary thrombosis cerebral thrombosis arterial embolism and venous thrombosis and those suffering from Buerger s disease

In commenting upon their personal experience with this test Hagedorn and Barker (375) state we cannot say whether the heparin tolerance test as applied by us can be used to determine the presence or absence of a tendency to intravascular thrombosis but we believe there is significance in the relatively high incidence of non reactors and hyporeactors among the patients who had intravascular thrombosis However further study of a larger series of cases of thrombosis of various types is indicated

Waugh and Ruddick (376 377) have reported a test for increased coagulability of the blood based on controlled deceleration of the clotting mechanism through the addition of heparin to the blood in vitro Using this test they demonstrated an increased coagulability of the blood under a wide variety of circumstances including various acute infectious processes postoperatively and following hemorrhage

Ogura and his associates (378) using the Waugh Ruddick test found that in 77 8 per cent of 27 cases of coronary thrombosis there was a decreased coagulation time evident by the 2nd or 3rd day following the acute thrombosis and lasting into or through the 3rd week thereafter Hagedorn and Barker (379) compared the

the number and severity of thromboembolic complications in a selected patient population We should not be surprised therefore to encounter an occasional thromboembolic episode in the presence of apparently adequate anticoagulant therapy As a matter of fact it is somewhat surprising that the anticoagulants do not more often fail to prevent or ameliorate thromboembolic phenomena

Hypercoagulability of the Blood

There is considerable evidence that a definite hypercoagulability of the blood predisposes certain persons to the development of thromboembolic phenomena Such persons are found commonly among those who suffer from obliterative vascular disease coronary artery disease and similar cardiovascular conditions among persons bedridden following major surgery childbirth trauma and because of debilitating chronic diseases and in certain others The common denominators of these conditions are that there is a disturbance of one sort or another in the blood vascular system and a particularly high incidence of thromboembolism Unfortunately it has not been demonstrated convincingly that such hypercoagulability of the blood occurs consistently in these conditions or that it is necessarily the precursor of a thromboembolic episode

Hyperprothrombinemia

Shapiro and others (218 299 307 370 371) have shown that hyperprothrombinemia as indicated by a shortening of the prothrombin clotting time to below the normal range may occur in man during the developmental stage of intravascular thrombosis and in man and animals following the administration of vitamin K (360 361 372) It is necessary ordinarily to employ 12 5 per cent diluted plasma in determining the prothrombin clotting time in order to demonstrate this hyperprothrombinemia

Shapiro (299) has observed reactive hyperprothrombinemia in acute thrombophlebitis and in pulmonary infarction but not in arterial thrombosis embolism other than that of the pulmonary vessels or in acute coronary occlusion In acute coronary occlusion and in peripheral arterial embolization prothrombinemia was the rule He has utilized the presence or absence of hyperprothrom

against thromboembolism is the failure to recognize the potential hazard and so to delay the institution of anticoagulant therapy. If heparin is used alone it must be continued during the entire period during which thromboembolic complications are anticipated, in most instances for 4 weeks after the last thromboembolic complication.

DICUMAROL (381)

Anticoagulant therapy with dicumarol may fail to prevent the occurrence of thromboembolic phenomena under any one of the following circumstances:

(1) The maximum prolongation of the prothrombin clotting time does not ordinarily occur for from 48 to 72 hours after the administration of a single dose of dicumarol (37). There is ordinarily a latent period somewhat shorter than this during which there is no significant prolongation of the prothrombin clotting time at all. If we accept the view that the anticoagulant effect of dicumarol is reflected by the prolongation of the prothrombin clotting time, one may not expect to obtain therapeutic prothrombin levels in a patient for the

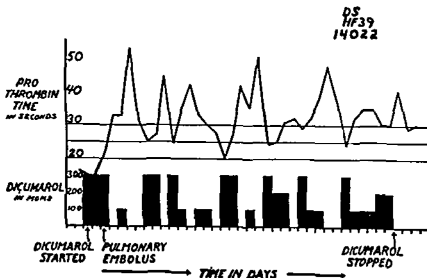


FIGURE 19. Thromboembolic complication occurring during the initiation of dicumarol therapy but before the prothrombin clotting time had been adequately prolonged.

results of this test with those of the heparin tolerance test and concluded that the results of the heparin tolerance test can be closely duplicated by testing the coagulation time of blood added to heparin in vitro immediately after withdrawal if the concentration of heparin is approximately the same The coagulation time of heparinized blood in vitro is a simpler test Silverman (380) using a modification of the test which employs recalcified plasma instead of whole blood found that in patients undergoing major surgical operations there is an increased coagulability of the blood present within 24 hours postoperatively and that this condition persists for from 1 to 2 weeks

As a practical matter however the failure of anticoagulant therapy to prevent the occurrence of thromboembolic phenomena is most often the result of any one or more of three errors on the part of the physician in prescribing these drugs namely

(1) A delay in the institution of anticoagulant therapy
(2) Failure to obtain or to maintain an adequate level of effectiveness during the period of administration and
(3) The premature discontinuation of the anticoagulant

Optimal medication is not attained without painstaking evaluation day by day but the technique is simple enough if the physician understands the significance of adequate therapy

HEPARIN

The current trend is to use dicumarol for anticoagulant therapy in a majority of those cases which require such medication for more than a few days Heparin is being used increasingly only during the first few days of anticoagulant therapy until such a time as the full effect of dicumarol has been attained Heparin acts so promptly that there is ordinarily no difficulty in obtaining satisfactory prolongation of the coagulation time within a matter of a fraction of an hour after its administration Following the initial dose of heparin bedside determination of the coagulation time should be done at intervals of about 1 hour to ascertain that the coagulation time has been prolonged at least three to sixfold and that it has not returned to normal level inside of 3 or 3½ hours Subsequent checks should be made on 1 or 2 occasions daily

The most common reason for failure to protect the patient

bin clotting time is not influenced appreciably when the coagulation time is no longer than about 12 minutes Ordinarily when heparin is being administered intermittently by the intravenous route the coagulation time of the whole blood will have been shortened to 10 to 12 minutes within 3½ hours It is advisable then to obtain samples of blood for the prothrombin clotting time just prior to the administration of a dose of heparin

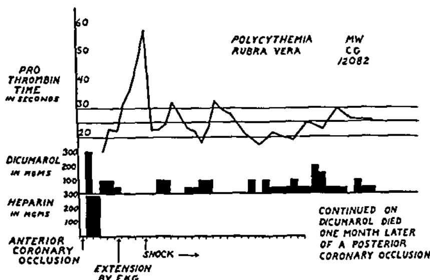


FIGURE 20 Thromboembolic complication (extension of myocardial infarct) occurring during the initiation of anticoagulant therapy in the interval between the withdrawal of heparin and the adequate prolongation of the prothrombin clotting time by dicumarol

(3) At this time there is not complete agreement on the extent to which the prothrombin clotting time must be prolonged to completely protect the patient against thromboembolism nor on the need for maintaining such levels over a period of time We have been impressed by the frequency with which thromboembolic complications occurring during the administration of dicumarol have coincided with relatively short prothrombin times This has been true whether the patient has been maintained at relatively slight prolongations of the prothrombin time or whether there has been a temporary fall in an otherwise considerably prolonged prothrombin time

We have made a preliminary review of those cases in the

first 2 or 3 days following the administration of even an adequate initial dose of dicumarol alone. In other words, one cannot hope to reduce the incidence of thromboembolic complications consistently until dicumarol has had sufficient time to reduce the prothrombin activity of the plasma to a level which is effective in interfering with intravascular clot formation.

An example of the occurrence of a thromboembolic complication during the period of initiating dicumarol therapy is illustrated in Figure 19. Despite the administration of 300 mg. of dicumarol on each of the first 3 days of therapy, a pulmonary embolus occurred on the 3rd day. At the time the embolus occurred, the prothrombin clotting time had not yet been prolonged to 25 seconds (25 per cent of prothrombin activity). The embolus may have arisen from a preexisting venous thrombus.

(2) To reduce the risk of thromboembolism to a minimum during the initiation of dicumarol therapy, it is necessary to administer heparin concurrently and in adequate amounts. Heparin must not be discontinued arbitrarily, but only after the prothrombin clotting time has been prolonged adequately, since if the anticoagulant effect of the heparin is lost before that of the dicumarol is sufficient to protect the patient, thromboembolic phenomena may occur during the interval in which neither drug is effective (333).

This situation is illustrated by the patient in Figure 20, from whom heparin was withheld after it had been administered for 18 hours. Because dicumarol had been given in relatively small doses after the 1st day, the prothrombin clotting time was not prolonged sufficiently until the 6th day. On the 5th day, when the prothrombin clotting time was still shorter than 25 seconds, there was an extension of the area of myocardial infarction, manifested clinically and confirmed by alterations in the electrocardiogram.

Therefore, when it is necessary to protect the patient immediately against thromboembolic phenomena, both heparin and dicumarol are to be administered concurrently in full therapeutic doses, and heparin is not to be withheld until the prothrombin clotting time of the blood has reached a level which is considered adequate therapeutically.

When heparin and dicumarol are being administered to a patient at the same time, it is important not to take samples of blood for determining the prothrombin clotting time while the coagulation time of the whole blood is significantly prolonged by the action of heparin. It appears that the prothrom

agreement with Allen and his associates of the Mayo Clinic who advocate the reduction of prothrombin activity to 20 per cent of normal We do not agree with those who feel that the patient has optimal protection from thromboembolic complications with reductions in prothrombin activity to between 40 and 50 per cent of normal (172)

(4) Anticoagulant therapy must be continued for that period of time during which the hazard of thromboembolism

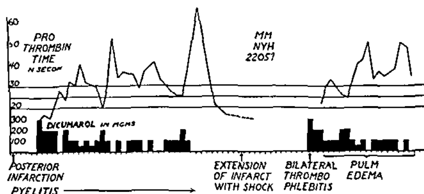


FIGURE 23 Thromboembolic complications occurring following withdrawal of dicumarol Anticoagulant resumed immediately upon recognition of thrombophlebitis

is great This period will vary from patient to patient depending upon a variety of circumstances and no arbitrary time limit may be set for the discontinuation of the anticoagulants However there is considerable evidence supported by our data on thromboembolism following coronary occlusion with myocardial infarction that anticoagulants should be given for at least 25 to 30 days after the most recent thromboembolic complication

The occurrence of thromboembolic complications immediately or very shortly after the premature discontinuation of dicumarol has been observed repeatedly This is demonstrated by the case in Figure 23 in whom there was an extension of the original myocardial infarction immediately and the development of a bilateral thrombophlebitis shortly after the termination of dicumarol therapy

A J Quick (150) has made some interesting observations in this connection He discovered that a heart puncture performed on a rabbit with a reduced prothrombin activity would produce

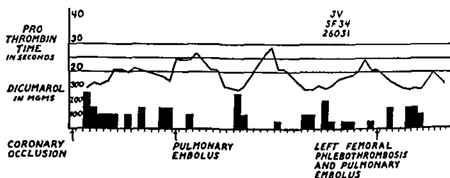


FIGURE 21 Thromboembolic complications (pulmonary emboli and phlebo thrombosis) occurring when the prothrombin clotting time was insufficiently prolonged

current American Heart Association study in which thrombo embolic complications occurred during dicumarol therapy This review reveals that of the 38 complications observed during the course of dicumarol therapy only 4 occurred in patients whose prothrombin clotting times are known to have been maintained at levels of 30 seconds or above (prothrombin activity reduced to 20 per cent or less of normal) for at least the 3 days preceding the appearance of the complication (225)

The occurrence of multiple thromboembolic phenomena in a patient treated with dicumarol but in whom the pro thrombin clotting time is not prolonged to the degree recom mended is illustrated in Figure 21 In sharp contrast is the case portrayed in Figure 22 in whom dicumarol was admin istered in amounts sufficient to maintain the prothrombin clotting time within the recommended range for almost the entire period of anticoagulant therapy We are in complete

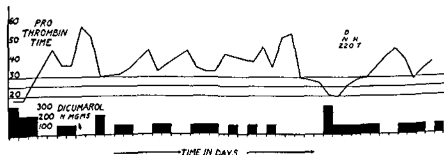


FIGURE 22 Prothrombin clotting time maintained at adequately prolonged levels for the greater portion of six weeks

CHAPTER 18

The Abuses of Anticoagulant Therapy

ONE MUST conclude that the greatest weakness in the clinical application of the anticoagulants today is the human element *Unfortunately, both heparin and dicumarol are therapeutic agents which require meticulous care in order to achieve successful therapeutic results without producing hemorrhage*

As has been emphasized repeatedly by E V Allen (164) neither heparin or dicumarol are ideal anticoagulants Actually they fall far short of the mark They cannot be ordered and administered with the abandon which characterizes the current usage of sedatives analgesics and antibiotics Too many physicians criticize the anticoagulants for the shortcomings which demand this painstaking administration

In the vast majority of specific instances brought to our attention where anticoagulant therapy has failed to accomplish its purpose or where it had led to bleeding it has been obvious that *the fault rested with the physician who administered the drug* For example dicumarol is often administered to a patient before the prothrombin clotting time has been determined Less frequently dicumarol is administered over a period of days without the prothrombin clotting time being determined at any time Instances of serious bleeding and of fatal bleeding occurring under such circumstances has already been mentioned in Chapter 16 in connection with the reports of Abramson (336) Fahraeus (337) Draper (342) Thorson (343) and Shlevin and Lederer (344) It is true that difficulties may arise from the peculiarity of response by a particular patient or from erroneous work in the laboratory but in the final analysis it is the responsibility of the physician to recognize that such instances may arise and to guard against them

It must be repeated that there is no rigid rule for administering anticoagulants Each patient responds differently and any patient

fatal hemopericardium To 5 of 6 rabbits whose prothrombin times were 6 seconds before treatment he gave dicumarol in amounts of 2 mg per kg of body weight daily by stomach tube Each day he performed a cardiac puncture with a #21 needle Fatal hemopericardium occurred in 2 animals on the 2nd day in 2 animals on the 3rd day and in the remaining animal on the 4th day In all instances where cardiac puncture was performed on an animal whose prothrombin time was 19 seconds or less the animals survived In every instance where the cardiac puncture was performed on an animal whose prothrombin clotting time was 24 seconds or more fatal hemopericardium occurred According to the prothrombin activity curve obtained by Quick on rabbit plasma using his one stage method these temporal values represent 17 and 12 per cent of normal prothrombin activity respectively

Quick cites his experience with cases of idiopathic hypoprothrombinemia Those patients with prothrombin times of 16 seconds (approximately 45 per cent of normal prothrombin activity[1]) had no hemorrhagic tendency 2 cases with prothrombin clotting times of 19 seconds (approximately 30 per cent of normal[1]) exhibited a distinct bleeding tendency while 1 patient with a prothrombin clotting time of 30 seconds (approximately 15 per cent of the normal[1]) had a very severe hemorrhagic condition Quick concludes that hemostasis depends upon the amount of thrombin formed and when prothrombin activity is reduced to about 20 per cent of normal insufficient thrombin is furnished for stanching

These figures for percentage of prothrombin activity are determined from the prothrombin activity curve obtained by Quick using his original technique and thromboplastin obtained from rabbit brain The prothrombin time obtained on normal whole plasma is 12 to 13 seconds

That dicumarol can often be safely administered to patients who are apparently poor risks is demonstrated by the case in Figure 24 This patient had longstanding renal disease of a complex nature Renal calculi with left sided hydroureter and hyronephrosis had existed for 5 years There was impaired renal

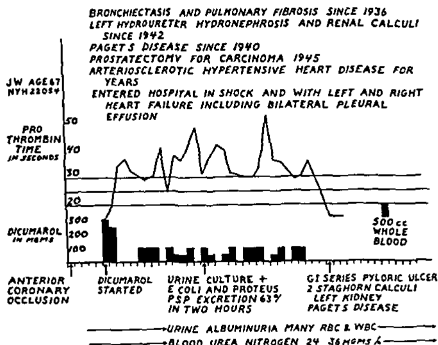


FIGURE 24 Administration of dicumarol despite multiple complicating pathological conditions Adequate prolongation of the prothrombin clotting time was maintained for over one month without producing hemorrhage

function and the urinary sediment contained leukocytes and erythrocytes in moderate numbers A prepyloric gastric ulcer was demonstrated radiographically Additional diagnoses which revealed conditions aggravating the patient's poor risk included bronchiectasis with pulmonary fibrosis Paget's disease and hypertensive cardiovascular disease with both right and left sided heart failure and bilateral pleural effusions Despite the considerable risk dicumarol was administered to this patient for at least 30 days and the prothrombin clotting time of his whole

may respond differently from day to day as for example during recovery from congestive heart failure or dehydration or uremia Thus only by considering the condition of the patient the prothrombin level the trend of the prothrombin curve and the previous response of the patient can the daily dose of anti coagulant be ordered There are specific contraindications to the use of the anticoagulants but the patients these involve are relatively few in number Finally when patients are treated with dicumarol on an ambulatory basis there are always the additional risks that the patient will not follow instructions carefully or that he may suffer accidental trauma which may lead to serious hemorrhages

The responsible physician must understand the use of the anticoagulants and their control by the laboratory sufficiently well so as to be able to recognize erroneous laboratory reports These may occur as a result of carelessness in obtaining samples of blood in preparing the thromboplastin mixture or in de termining the prothrombin clotting time More often they occur because the laboratory has failed to develop a consistently repro ducible technique or because of variations in the potency of the thromboplastin Prothrombin activity curves which are not cor rectly obtained or which cannot be interpolated are very common sources of consistent error in reporting percentage of prothrombin activity (174)

Finally the physician must learn from experience

(1) How these drugs act and their limitations
(2) The rationale of obtaining an adequate therapeutic level
(3) The hazard of too intensive anticoagulant therapy
(4) Where to look for hemorrhagic manifestations and
(5) How to treat these promptly and efficiently

In this way many well trained physicians have demonstrated that therapeutic successes can be the rule and complications the exception

Since the thromboembolic diseases are serious conditions with death rates frequently exceeding 20 per cent and with a high incidence of crippling and debilitating residual effects the hazard of anticoagulant therapy to a patient presents a small but calcu lated risk

SECTION VIII

PHYSIOLOGICAL AND PHARMACOLOGICAL INFLUENCES

plasma was maintained at levels between 30 and 50 seconds There was no bleeding outside of the urinary tract and the number of erythrocytes in the urinary sediment did not increase during anticoagulant therapy Such a patient must be handled judiciously and must be observed carefully during the entire period of anticoagulant therapy

CHAPTER 19

Physiological Variations in the Prothrombin Test

LINK (382) has listed conveniently the factors known to influence the response to dicumarol in standardized susceptible assay animals whose body weight age sex and other factors are under rigid control Three of these factors the levels of vitamins C and K in the diet and in the body reserve the hepatic and renal functions and in females pregnancy and lactation have been discussed previously in Chapter 11 in relation to the use of dicumarol in man

Two factors the influence of the methylxanthines and of digitalis and the production of hypoprothrombinemia by salicylates will be discussed in the next chapter Those which remain the age and sensitivity of the animal and the nutritional status of the subject along with certain other physiological variations will be discussed briefly in the following paragraphs

INDIVIDUAL SENSITIVITY

A very marked variation in the sensitivity of individual rabbits to dicumarol was observed first by W K Smith (383 384) and was shown to be due in part to a variation inherited as a Mendelian character by Campbell (385) Variation in response to the oral administration of dicumarol occurs also because of variations in the ability of the animal to absorb the substance from the gastrointestinal tract In contrast Link and his coworkers did not observe relative resistance to dicumarol in rats guinea pigs or dogs He mentions that the horse does not develop the hemorrhagic sweet clover disease from the eating of spoiled sweet clover Since the rabbit does not acquire an immunity to dicumarol it is possible to use the assay rabbits repeatedly after permitting a short period of recovery from any given experiment

Overman Newman and Wright (390) have recently reinvestigated this matter on 25 presumably normal young adults The prothrombin clotting times were determined by the Link Shapiro modification of the one stage technic and the thromboplastin used was obtained from rabbit lung Observations were made daily for periods of from 10 to 40 weeks The prothrombin times were determined by 3 different individuals and no values were discarded In 828 determinations on whole plasma the mean prothrombin time was 15 8 seconds and the standard deviation ±1 22 seconds In 813 determinations on 12 5 per cent diluted plasma the mean prothrombin time was 38 6 seconds and the standard deviation ±2 16 seconds The range of prothrombin clotting times was 12 to 18 seconds for whole plasma and 32 to 42 seconds for 12 5 per cent diluted plasma

To determine the variations between individuals these workers analyzed 13 prothrombin readings on plasmas from each of 15 presumably normal persons a total of 195 readings by the method of analysis of variables This was done for both whole (undiluted) and 12 5 per cent diluted plasmas The variability between individuals was found to be significantly greater than the variability between repeated prothrombin determinations on the same individual although the findings with 12 5 per cent plasma were less significant than were those with undiluted plasma Inspection of the original data indicates clearly that individuals differ in their normal prothrombin clotting times When the 13 readings on each of the 15 individuals were averaged there were variations of as much as 2 seconds for undiluted plasma and as much as 5 seconds for 12 5 diluted plasma No attempt was made in this study to correlate these variations with age sex or other potential variables

Variations According to Time of Day

Tanturi and Banfi (391) concluded that the prothrombin clotting time for normal persons is constant and does not vary with time of day Levan (340) however noted that the prothrombin clotting time determined on samples of plasma obtained after breakfast were higher than those obtained on fasting specimens Meyers and Poindexter (371) found a tendency of the prothrom

Daily Variations in Prothrombin Clotting Time

Variations in the prothrombin clotting time of whole and diluted plasma from normal individuals have been studied from day to day by several observers but the results are somewhat conflicting and the interpretations differ widely due in part to the variations in the methods employed in the determinations

Quick (241) stated in 1942 that the prothrombin concentration in the blood of normal healthy adults is remarkably constant *Hause and Tocantins (386) using the one stage method de*termined the prothrombin clotting time of 3 healthy men for 53 consecutive days They found that the mean clotting time of whole plasma was 19 5 seconds with a standard deviation of ±0 903 second They observed also that certain normal individuals have consistently high prothrombin values Cotlove and Vorzimer (218) studied the prothrombin clotting times of 35 normal subjects using the Link Shapiro modification of the one stage method and a thromboplastin obtained from rabbit lung They obtained a mean clotting time for whole plasma of 15 5 seconds with a standard deviation of ±1 5 seconds Aggeler et al (387) determined the plasma prothrombin clotting time on 30 normal subjects by the one stage method but utilized a thromboplastin obtained from human brain They found a mean clotting time of 11 5 seconds with a standard deviation of ±0 73 second

Martin Curfman and Cavano (388) using Brambel s modification of the one stage method and 3 different batches of thromboplastin found in a group of 93 normal people that the mean clotting time was 17 2 seconds with a standard deviation of ±0 6 second The range of variation among these normal subjects was 3 seconds They found that the prothrombin times obtained with the use of 12 5 per cent diluted plasma were much less consistent having a standard deviation of 10 seconds and a range of normal from 56 to 115 seconds They conclude that moderate variations in the prothrombin clotting times as obtained by this method are of doubtful significance

Nitshe Gerarde and Deutsch (389) applied a fibrinogen dilution technic to serial plasmas obtained from normal subjects and found that there was considerable variation in the prothrombin clotting times obtained

The Effect of Diet

Tocantins and O Neil (391) noted pronounced increases in prothrombin activity as determined by Quick s method in both dogs and humans following the ingestion of protein rich meals Warner Brinkhous and Smith (97) observed variations in the prothrombin clotting times obtained on dogs who were fed widely different diets but the results were within the limits of experimental error

Pohle and Stewart (301) observed that grossly lipemic plasma tended to have short prothrombin clotting times Using the Quick method they found that the prothrombin clotting time tended to be shorter following the ingestion of a meal heavy in fat Martin Curfman and Cavano (388) were unable to show any difference in the prothrombin clotting times obtained on undiluted samples of plasma taken 2 hours after an average breakfast containing 20 to 30 grams of fat and those taken before and 2 hours after a breakfast containing 50 grams of fat

To ascertain if a diet high in cholesterol would influence the prothrombin clotting time Overman Newman and Wright (390) gave 4 subjects 6 eggs a day in addition to their regular diet and determined the prothrombin clotting time daily for 4 weeks In 66 prothrombin determinations on whole and on diluted plasma mean values of 16 4 seconds and 39 1 seconds respectively were obtained The variation was less than that encountered in normal individuals

MENSTRUATION

We have observed repeatedly that some women patients who are treated with dicumarol require a somewhat greater amount of dicumarol to maintain a given prolongation of the prothrombin time during menstruation than during the interval between menses Brambel (392) has observed that just preceding and during menstruation there is an increase in the prothrombin activity of the plasma which may be demonstrated when the prothrombin clotting time is determined using 12 5 per cent diluted plasma Hause and Tocantins (386) using the one stage method and whole plasma found no consistent change in the prothrombin level during the menstrual cycle

It is of interest that O W Smith and G V Smith (393) have

bin clotting time in patients with coronary arteriosclerosis to drop after midnight but they did not observe this phenomenon in 6 normal males studied as controls

Martin Curfman and Cavano (388) ran serial determinations of the prothrombin clotting time on ambulatory patients through the day using the Link Shapiro method They did not find any significant difference between bloods drawn before or after breakfast but they did find a consistent lengthening of the prothrombin clotting times obtained on specimens drawn in the midafternoon as compared with the times obtained on morning specimens

Overman Newman and Wright (390) obtained samples of blood at different times of day from 9 individuals over a period of 3 weeks One hundred prothrombin clotting times were performed on blood samples taken before breakfast 109 on samples obtained after breakfast and 115 on samples obtained after lunch When compared statistically variations were found to be slight somewhat inconsistent and of doubtful significance for clinical purposes They concluded that if the relation between the time of obtaining samples of blood for prothrombin determinations to meals has any effect on the prothrombin values obtained it must be small at best

The Effect of Exercise

There are 2 studies which indicate that exercise has no effect on the prothrombin clotting time of the plasma Meyers and Poindexter (371) using the Link Shapiro technic could detect no change in the prothrombin clotting time following toe touching exercises by 5 normal males and 5 patients recovering from coronary occlusion Overman Newman and Wright (390) studied the effect of exercise on 10 subjects Blood samples were obtained before and after these subjects had run down and back up 5 flights of stairs The tests were performed on the same day and under identical conditions The mean prothrombin clotting time of 34 determinations performed before exercise was 17 09 seconds for whole plasma and 39 65 seconds for diluted plasma The mean prothrombin clotting time of 34 determinations performed on blood obtained after exercise was 17 03 seconds for whole plasma and 39 6 seconds for diluted plasma The differences are not significant statistically

CHAPTER 20

The Effect of Certain Drugs on the Blood Coagulation and on the Prothrombin Time

SALICYLATES

LINK and his associates (37 394 395) first demonstrated that the salicylates possess the property of inducing hypopro thrombinemia When they administered a single dose of salicylic acid orally or intravenously to rats fed a diet low in vitamin K a temporary hypoprothrombinemia occurred When the rats were fed a natural grain ration or one containing 2 methyl 1 4 naphthoquinone salicylic acid failed to induce hypoprothrom binemia It was thus demonstrated that vitamin K counteracts this particular effect of the salicylates The hypoprothrombinemia produced by salicylates could be demonstrated by the use of 12 5 per cent diluted plasma before changes were observed in the prothrombin clotting time of the whole plasma The coagulation time of the whole blood was ordinarily unaffected Hemorrhage did not occur unless the salicylates were fed or injected contin uously over periods of time

The similarity of the hypoprothrombinemia induced by salicylates and that induced by dicumarol was obvious though in the rat the potency of salicylic acid was only about one twentieth that of dicumarol Salicylic acid was obtained by the quantitative chemical degradation of dicumarol in vitro but no comparable degradation was demonstrated in vivo There was evidence that the salicylates acted as anticoagulants in vitro

The ability of the commonly used salicylates to produce hypo prothrombinemia in man was demonstrated promptly by a num ber of observers Meyer and Howard (396) administered sodium salicylate and acetylsalicylic acid orally to human subjects in doses of 1 3 to 5 3 grams daily and found that the plasma prothrombin clotting time was prolonged consistently The simultaneous ad ministration of vitamin K prevented this effect

shown that the blood of women during menstruation and in certain instances of toxemia of pregnancy has marked fibrinolytic activity evidently due to the elaboration of a proteolytic enzyme which may affect the clotting and bleeding times It is common experience that the menstrual flow may be increased in patients who are receiving dicumarol at the time of menses

The influence of pregnancy and lactation upon the prothrombin clotting time and the relation of this to the administration of dicumarol has been discussed in Chapter 11

epistaxis or hemorrhages into the nail beds occurred at the time of maximum prothrombin depression Clausen and Jager (410) have also reported an instance of bleeding from nose and gums during hypoprothrombinemia induced by salicylates Heindl Anderson and Friedlander (411) have reported thrombinemia in which salicylate therapy may have been a factor

Neuvert (412) has ascribed the occurrence of late postoperative hemorrhage following tonsillectomy to hypoprothrombinemia brought about by the use of salicylates and has advocated the con current administration of vitamin K if salicylates are administered to patients undergoing tonsillectomy

Quinine and Quinidine

Pirk and Engelberg (413) reported in 1945 that when quinine sulphate or hydrochloride was administered orally to normal human subjects a hypoprothrombinemia was induced which could be prevented by the concurrent administration of synthetic vitamin K Prothrombin clotting times were determined by the method of Page (303) utilizing Russell viper venom as the thromboplastic agent

Two to 4 prothrombin determinations performed on each subject prior to the administration of quinine gave values within the range of normal variation When quinine sulphate or hydro chloride was given orally in single daily doses of 0 33 gram the prothrombin clotting times were prolonged by from 5 to 11 8 seconds When after 6 to 16 days of medication the quinine was discontinued the prothrombin clotting times fell to approxi mately the control values in a few days Subsequently subjects were given both quinine sulfate 0 33 gram a day and Synkavite 10 mg a day concurrently The concurrent administration of vitamin K protected all subjects against the development of hypo prothrombinemia Subsequently quinine sulfate in daily doses of 0 33 gram was given alone to 2 of these subjects for a period of 7 to 8 days and again the prothrombin clotting times were pro longed

The authors concluded that the prolonged administration of quinine in large doses might interfere with the normal process of blood coagulation They stated further that quinidine has a

Shapiro, Redish and Campbell (397) confirmed the fact that adequate doses of salicylates produce a hypoprothrombinemia in rats and in man and that this hypoprothrombinemia can be prevented by the administration of vitamin K provided that liver function is adequate. They also confirmed:

(1) That the hypoprothrombinemia is most readily demonstrated by the use of diluted plasma;

(2) That the level of vitamin K intake has a considerable influence on the degree and duration of the hypothrombinemia; and

(3) That the effect of salicylate is augmented in the presence of preexisting hypoprothrombinemia or hepatic damage.

Shapiro (398) showed that patients receiving 5 to 6 grams of salicylic acid daily developed hypoprothrombinemia after 3 to 5 days of therapy, but that menadione in doses of 2 to 9 mg daily protected against this hypoprothrombinemia. Zimmerman and Shapiro (399) have shown subsequently that the addition of 1 mg of menadione and 100 mg of ascorbic acid to each gram of salicylate administered will maintain the prothrombin time at normal levels without altering the salicylic acid concentration of the plasma.

Coombs, Higley and Warren (400) and Butt et al. (401) reported that patients with rheumatic fever receiving 6 to 10 grams of sodium salicylate daily developed moderate prolongations of the prothrombin clotting time, but did not exhibit spontaneous hemorrhage.

Fashena and Walker (402) found that moderate as well as large doses of sodium salicylate induce hypoprothrombinemia regularly, but that this hypoprothrombinemia may regress spontaneously to some extent even though salicylate therapy is continued. This spontaneous regression was confirmed in infants and children by Govan (403) and in adults by Rapoport, Wing and Guest (404).

Petechial hemorrhages due to thrombocytopenia attributable to salicylate therapy have been reported (405, 406), as has frank purpura (406, 407) and death from hemorrhage (408). Owen and Bradford (409) have reported hypoprothrombinemia of varying degree occurring in 25 cases of acute rheumatic fever treated with massive doses of sodium salicylate and in 5 of these patients

quinine can be demonstrated when viper venom is used as the source of thromboplastin but not when a rapidly acting thrombo plastic tissue extract is used They believe that the ability of vitamin K to reverse the effect of quinine is proof that hypo prothrombinemia does occur

Clark and Spitalny (416) reported in February 1946 that a number of antipyretic drugs are able to produce a hypoprothrom binemia Clark (417) has subsequently studied the hypopro thrombinemic effect of quinine on rats fed stock diets Link s low vitamin K diet and 20 per cent mineral oil in powdered dog blocks Quinine was administered orally for 3 to 4 days in doses up to 200 to 400 mg per kg body weight The prothrombin time was determined by the method of Link and Campbell using a dried rabbit brain extract as the source of thromboplastin usually on 20 per cent diluted plasma No hypoprothrombinemia was demonstrated following the administration of quinine

Poindexter and Meyers (418) gave 1 0 gram of quinidine orally to 10 patients with coronary arteriosclerosis and determined the prothrombin clotting time after 1 and after 3 hours by the Shapiro modification of the one stage method using both whole and 12 5 per cent diluted plasma There was no effect on the prothrombin time as determined on either the whole or dilute plasma We have used quinidine in doses of as much as 2 5 to 5 5 grams a day for the restitution of normal cardiac rhythm simultaneously with the administration of dicumarol without encountering any diffi culty in the management of the anticoagulant

THE XANTHINES

Nonnenbruch and Szyszka (419) discovered that the coagula bility of the blood was increased in rabbits following the intra venous injection of theophyllin and ethylenediamine Studies by these authors and by others (420-423) confirmed the original observation and led to the recommendation that this drug be used as a coagulant in cases of hemorrhagic diathesis Subse quently Sirasaka (424) has reported that the administration of caffeine shortens the bleeding time in rabbits

Link and his associates studied extensively the effect of the methylxanthines on the prothrombin clotting time of experi

similar action though offered no evidence in support of this statement

Quick (414) administered the same daily dose of quinine sulfate (0 33 gram) orally to 4 normal young adults for 8 days Prothrombin clotting times were determined on both undiluted and on 20 per cent diluted plasma by Quick s one stage method utilizing thromboplastin obtained from rabbit brain He could not demonstrate any reduction in prothrombin activity Quick suggested that the difference in results between his study and that of Park and Engelberg may have resulted from the use of different thromboplastic substances

Prompted by Quick s contrary results Park and Engelberg (415) repeated their initial work on 2 subjects and again found that when quinine was administered alone the prothrombin clotting time was prolonged but that when both quinine and vitamin K were administered the prothrombin time was unchanged They then checked the 2 methods of determining the prothrombin time against each other on normal subjects but modified the Quick technic by using a commercial thromboplastin obtained from rabbit lung Control values were obtained by running the prothrombin clotting time in duplicate by each method on each of 3 days The average of the 6 values so obtained was considered to be the premedication value for each subject by the particular method used

Although the duplicate values for a given method checked well there was considerable difference between the results obtained by the 2 methods on each patient When quinine was given to each subject in daily doses of 0 33 gram for from 4 to 11 days hypoprothrombinemia was manifested by the Page method (using Russell viper venom) in from 1 to 9 days but no change in the prothrombin clotting time was demonstrated by the use of the Quick method When quinine and vitamin K were administered concurrently there was no change in prothrombin activity when determined by the method of Page When quinine was administered alone subsequently hypoprothrombinemia was again demonstrated by the method of Page but not by the method of Quick

The authors concluded that the prothrombinopenic effect of

demonstrated by the use of highly diluted plasma which he considered to be highly artificial and empirical

Scherf and Schlachman (429) studied the prothrombin clotting time and the plasma coagulation time in man following the injection intravenously of theophyllin and ethylenediamine (aminophyllin) or theophyllin with sodium acetate and after the oral administration of several methylxanthines Their subjects were free of hepatic disease or other condition which might influence blood coagulation Prothrombin times were determined in duplicate by the Fullerton modification (430) of the Quick one stage method and a mean calculated Plasma coagulation times were determined by a modification of Cheney s method (431) Control values were obtained before the administration of medication and serial determinations were made 1 2 3 and 24 hours after intravenous administration and daily for 5 days after oral administration

When 0 5 gram of aminophyllin was injected intravenously into 22 subjects the prothrombin clotting times were shortened in all but 1 subject by from 1 2 to 9 5 seconds but exceeding 3 seconds in 14 instances There was a distinct reduction in the prothrombin clotting time in 18 of 21 subjects after 1 hour The maximum effect occurred in from 1 to 3 hours but values were returning to normal after 6 hours in those cases followed this long The plasma coagulation time was shortened in 18 of 20 cases and in 15 of these the shortening was greater than 1 minute It was definite after 1 hour in 10 of 18 cases but the maximum effect occurred in from 2 to 24 hours It was returning to normal in 16 cases and had reached the control value in 12 cases 24 hours after injection

When theophyllin with sodium acetate was injected intravenously into 12 subjects there was a shortening of the prothrombin clotting time in 11 instances Eight of the 12 subjects exhibited a shortened coagulation time but 4 subjects had an unexplained prolongation of the coagulation time There was no correlation between the prothrombin clotting times and the plasma coagulation times

The effect of the methylxanthines administered orally was studied by the use of theobromine 1 gram 3 times daily amino-

mental animals (37 394 425, 426) Campbell noted that when the purine bodies were removed from active concentrates containing dicumarol but free of vitamin K the ability of these concentrates to produce hypoprothrombinemia was enhanced out of proportion to that which might be expected if only inert materials were removed

Field and Overman showed that theobromine reduces the hypoprothrombinemic effect of the standard dose of dicumarol Field and Larsen demonstrated that large single doses of caffeine theophyllin and theobromine given orally to the dog rabbit or rat induce a state of hyperprothrombinemia readily detected when 12 5 per cent plasma is used but also demonstrable in whole plasma or whole blood The effect lasted for 5 to 7 days in the dog and rabbit but was of shorter duration and more variable in the rat

Field and Spero showed that if a standard dose of dicumarol be given to a dog along with the methylated xanthine the action of dicumarol is strongly suppressed If the methylated xanthine is given 24 hours after the dicumarol the extent of the hypoprothrombinemia is reduced and the duration is shortened The effect of the methylated xanthines is not due to their diuretic effect and they do not influence the prothrombin time when added to blood or to plasma in vitro In addition to producing a hyperprothrombinemia the methylxanthines produce an increase in the fibrinogen level of the plasma (426) The hyperprothrombinemia effect is restricted to the methylated xanthines but does occur with combinations of these drugs used clinically namely aminophyllin and theocine

Quick (427 428) gave single doses of 200 mg of caffeine theobromine or theophyllin to rabbits and to dogs and determined their prothrombin clotting times by his one stage method using whole plasma He found no increase in the prothrombin level of the plasma and no protection against the anticoagulant effect of dicumarol Quick concluded that the discrepancy in results probably resulted from differences in the technics for determining the prothrombin clotting time He questioned whether a true hyperprothrombinemia ever exists or can be produced and criticized the evidence for hyperprothrombinemia because it had been

Poindexter and Meyers (418) determined the prothrombin clotting time on whole plasma and on 12 5 per cent diluted plasma from 10 subjects following the oral administration of 0 8 gram of aminophyllin (3 grains 3 times during the preceding day 3 grains prior to performing the test) and found no change

Holland and Gross (434) injected dogs intravenously with 50 mg per kg of theophyllin sodium with glycine aminophyllin or dihydroxypropyl theophyllin and followed the prothrombin clotting times for 5 hours They then administered these same compounds to dogs by mouth in doses of 20 mg per kg daily for 13 days No significant change was observed in the prothrombin times or in the plasma clotting times When any 1 of the 3 drugs were given with dicumarol or when aminophyllin was given prior to the administration of dicumarol there was no less depression in the prothrombin activity than was produced by the administration of dicumarol alone Ten human subjects were given 500 mg of aminophyllin intravenously and the prothrombin time and plasma clotting time determined before and at 1 2 3 and 24 hours after injection No significant changes were obtained

In our own laboratory Overman (435) has administered doses of 600 mg to 1 gram of aminophyllin daily to 15 normal adults ranging in age from 25 to 35 years The aminophyllin was administered over periods of 3 to 4 weeks In two individuals doses of 1 8 grams daily produced toxic effects which necessitated discontinuance of the drug Prothrombin clotting times were determined on whole and 12 5 per cent diluted plasma by the methods of Quick and Link Shapiro using thromboplastin obtained from rabbit lung and by the method of Fullerton, using Russell viper venom Even in the doses provoking toxic reactions no significant changes were found in the prothrombin clotting times of these subjects Similar negative results have been reported by Rieben (436) and by Nitshe Gerarde and Deutsch (389)

DIGITALIS AND DIGITALOIDS

Coagulation Time

Macht (81 137) reported that when repeated samples of blood are taken from cats during intravenous injections of digitalis or ouabain solutions for purposes of assay the coagulation time of the blood samples as determined by Howell s method is progres

phyllin 0 5 gram 3 times daily or theobromine sodium acetate in enteric coated tablets 0 5 gram 3 times daily given to 14 subjects There was a significant shortening of the prothrombin clotting time in 10 of these 14 subjects and the average shortening in those with significant shortening only was 4 65 seconds The prothrombin clotting time was determined in 6 of the 14 subjects 24 hours after the ingestion of the drug and 3 revealed a hyperprothrombinemia at this time

Breytspraak and Greenspan (432) studied the effect of therapeutic doses of aminophyllin on the prothrombin time of young adult male patients with bronchial asthma who were under no other drug therapy at the time Prothrombin clotting times were determined on 12 5 per cent diluted plasma by the Quick method as standardized by Aggeler et al The thromboplastin was obtained from dehydrated human brain The authors standardized their technic by determining prothrombin clotting times on 10 normal individuals and then by determining the prothrombin clotting time on 10 separate specimens of blood from a single individual Five patients were given aminophyllin in doses of 0 1 gram orally 3 times a day for 7 days 4 patients were given 0 5 gram orally 3 times a day for 2 days and 3 patients were given single doses of 0 5 gram intravenously No significant changes in the prothrombin clotting time were detected

Gilbert Dey and Trump (433) carried out a series of experiments on human subjects and on animals determining the coagulation time of the blood by the capillary tube method and the prothrombin clotting time on whole and 12 5 per cent diluted plasma by the method of Quick and performing the heparin tolerance test of de Takats Aminophyllin was administered to human subjects intramuscularly and intravenously in doses of 0 5 gram every 2 hours or orally in doses of 0 2 gram 3 times a day for as long as 28 days Studies were also made on patients who had been taking methylated xanthines over periods of years Dogs were given aminophyllin in doses up to 135 mg 3 times a day for as long as 2 weeks The authors concluded— Prothrombin times were determined in the whole plasma and in the dilute plasma No change was found by either method Coagulation times were not affected The heparin curves were either not affected or were improved

De Takats Trump and Gilbert (82) studied the effect of digitalis on the clotting mechanism by means of the heparin tolerance test Their results indicated that digitalis antagonized the anticoagulant activity of heparin in both man and in experimental animals although they were unable to explain in mechanism of this action

Massie Stillerman Wright and Minnich (83) reported that the administration of digitalis causes a decrease in the clotting time of the blood In 35 patients of both sexes with and without heart disease and ranging in age from 24 to 78 years they could demonstrate no alteration in the prothrombin time nor in clot retraction determined before and after digitalization The general condition of the patient the degree of reaction to the drug or the presence or absence of heart failure had no detectable effect on the coagulation accelerating effect of digitalis

Moses (142) studied the response of 8 individuals to the intravenous administration of 0 15 mg of heparin per kg of body weight before during and after therapeutic digitalization Neither the coagulation time of the whole blood nor the response to heparin was significantly influenced

Sokoloff and Ferrer (84) studied 10 patients with heart failure who were able to tolerate a period of observation before digitalization The clotting time was determined by the three tube method of Lee and White daily for 4 days prior to digitalization The patients were then digitalized by oral administration according to the Eggleston method 6 patients to the point of minor toxicity Clotting times were then determined daily for 4 days thereafter The average clotting time before and after digitalization did not differ However the clotting times of individuals differed significantly regardless of therapy and the variations due to treatment were considerably less than those due to experimental error The experiment failed to support the view that oral digitalization increases the coagulability of the blood as determined by this technique

Prothrombin Time

Poindexter and Meyers (418) determined the prothrombin clotting time on whole plasma and on 12 5 per cent diluted plasma

sively shortened The same shortening of the coagulation time of the blood was observed in rabbits from which the blood samples were taken by heart puncture This thromboplastic effect was also manifested in vitro not only by digitalis and ouabain but also by all digitaloid glucosides obtainable it was not produced by numerous other drugs employed as controls with the exception of epinephrin and progesterone Assays on digitalis tincture made by the Hatcher cat method showed that the average lethal dose of digitalis for cats was definitely greater when the cats were previously given heparin by intravenous injection

Other investigators including Tanaka (using strophanthin) (438) Ramsey Pinschmidt and Haag (85) and Richardson and Walton (439) have found to the contrary that digitalis does not influence the clotting time of the blood in vitro Werch (440) found that when digifolin is injected into rabbits intravenously in comparatively large doses it causes a significant decrease in the coagulation time of the blood Tanaka (438) had previously reported the same effect when using strophanthin However Ramsey Pinschmidt and Haag (85) were unable to confirm that heparin had any influence on the toxicity of digitalis the lethal dose for their heparinized cats being the same as for the group receiving digitalis only

De Takats Trump and Gilbert (82) reported that digitalis had little effect on the coagulation time in the dog but that it did decrease the magnitude and duration of the heparin tolerance curve Richardson and Walton (439 441) injecting digitalis preparations intramuscularly into anesthetized dogs found that the extent of decrease in the coagulation time is not greater than that obtained in previous experiments without digitalis

Ramsey Pinschmidt and Haag (85) performed an extensive series of experiments on dogs In many of their experiments the results are complicated by the use of ether or barbiturate anesthesia which produced changes in the coagulation time However when 50 per cent of the fatal dose of digitalis was given as a single intravenous injection to unanesthetized dogs no reduction in coagulation time followed When dogs were given digitalis orally in daily doses sufficient to produce mild intoxication there was no effect on the coagulation time

course quite contrary to general belief and practice

Nay and Barnes (75) in their study of the incidence of thrombo embolic complications during the immediate convalescence from acute myocardial infarction noted that 8 out of 12 patients who received digitalis suffered thromboembolic phenomena Pulmonary embolism with infarction occurred in 5 of the 7 cases in congestive heart failure who received digitalis Among the 5 patients who were not in congestive heart failure but received digitalis 3 had thromboembolic complications Five of the 12 patients died and pulmonary embolism was the cause of death of 1 of these Total vascular complications in the 8 patients who suffered them were 12 in number pulmonary embolism 7 thrombophlebitis 2 and acute arterial occlusion 3 The authors conclude that because of the small number of patients who received digitalis they can only comment with interest on the role of digitalis in causing vascular complications

As has been mentioned in Chapter 4 in the series of 572 cases of recent myocardial infarction reviewed by Mintz and Katz (80) of those patients who suffered thromboembolic complications 20 received digitalis and 16 of these died a mortality rate of 80 per cent Of the 32 patients who suffered thromboembolic complications but did not receive digitalis 13 died a mortality rate of 40 6 per cent It is not clear from the report whether or not the most seriously ill patients received the digitalis

Mercurial Diuretics

Macht (137) has studied the effect of three mercurial diuretics mercupurin salyrgan and mercuhydrin on the process of blood coagulation in the rabbit the cat and the dog Mercupurin and salyrgan were employed without theophylline but mercuhydrin was employed in the solution as marketed in combination with theophylline When any one of these mercurials was injected intravenously or intramuscularly in doses of from 10 to 20 mg the clotting time of the whole blood as determined by Howell s method was very markedly accelerated The prothrombin clotting time was also definitely shortened and the heparin tolerance curve diminished in height and duration There was not in any instance an alteration in the blood platelet count or in the level

from 13 patients before and after administering a full digitalizing dose of digitalis There was no significant change in the prothrombin time Cotlove and Vorzimer (218) using both whole and diluted plasma found no alteration in the prothrombin time of 7 patients studied by them Massie Stillerman Wright and Minnich (83) obtained the same results However Peters Guyther and Brambel (211) stated that they were able to demonstrate repeatedly a decreased prothrombin clotting time upon the administration of digitalis but only by using 12 5 per cent diluted plasma They performed prothrombin determinations by the method of Quick using a modified thromboplastic reagent described by Brambel (305)

Clinical Reports

Askey and Neurath (443) studied the effect of digitalis in a group of 84 patients with auricular fibrillation among 1 247 patients with myocardial infarction admitted to the Los Angeles General Hospital Forty four patients received digitalis alone and 40 received either quinidine alone quinidine and digitalis or no medication at all Digitalis had no apparent role in producing sudden death or rupture of the heart In 48 patients with auricular fibrillation and congestive heart failure 32 were given digitalis alone Thirty one of these 32 patients (96 8 per cent) died in 13 instances of clinically recognized fatal embolism to the greater circulation Of the 16 patients with auricular fibrillation and congestive heart failure who received medication other than digitalis 11 died (68 7 per cent) in no instance of fatal embolism to the systemic circulation In the 36 patients without congestive heart failure *digitalis alone produced no greater incidence of* systemic embolism than did other types of treatment

Administration of digitalis alone seemed definitely associated *with increased mortality and with increased systemic embolism* in those with congestive heart failure but not in those without congestive heart failure The hazard of giving digitalis apparently was chiefly the hazard of embolism The authors conclude that on the basis of these data digitalis administered alone for congestive heart failure associated with auricular fibrillation and myocardial infarction would seem contraindicated This conclusion is of

peatedly for these experiments there was a permanent shortening of the coagulation time for long periods of time so that fresh animals had to be used Dicumarol administered by stomach tube antagonized and nullified the effect of the antibiotics Macht cites the report of Frada who attributed embolic accidents in 4 patients to an increased coagulability of the blood due to penicillin

Macht (447) in reporting his experiments in further detail states that penicillin shortens the coagulation time of the whole blood and the prothrombin time in animals and man that the thromboplastic effect of penicillin can be antagonized by suitable doses of dicumarol and that in animals the excessive prolongation of the prothrombin time and of the coagulation time produced by dicumarol can be corrected by the administration of penicillin He cites the statements of Pelz who has used penicillin as a blood coagulant before tonsillectomy (448 449)

Hines and Kessler (450) studied 10 patients before during and after the administration of penicillin in doses of 10 000 Oxford units every 3 hours to total doses of 140 000 to 2 5 million units There was no significant change in the prothrombin clotting time and according to the heparin tolerance test of de Takats there was a definite increase in the coagulation time in only 2 instances They suggested that penicillin may produce an increased reaction to heparin when the 2 drugs are administered together as in the treatment of subacute bacterial endocarditis

Lewis (451) studied the effects of penicillin on the blood of normal and hemophilic subjects both in vivo and in vitro The addition of various dilutions of penicillin to normal or hemophilic blood in vitro produced no effect on the coagulation time The intramuscular injection of penicillin in doses of 25 000 to 200 000 units had no effect on the coagulation time the clot retraction the prothrombin time platelet count bleeding time or fibrinogen concentration in either normal or hemophilic subjects

Overman (117 118) has reported that streptomycin hydrochloride and streptomycin sulfate prolong the prothrombin time and the coagulation time of blood in vitro However if strepto

of the blood calcium There was however a marked increase in the fibrinogen content of the blood

Macht states that clotting is accelerated following the injection of various other mercury compounds of an organic or inorganic nature He refers to the reports of Kaufman and of Silberman in which intravascular clots were described in cases of sublimate poisoning

Poindexter and Meyers observed that the intravenous ad ministration of 1 0 cc of mercupurin had no apparent effect on the prothrombin clotting times of whole or 12 5 per cent diluted plasma from 7 patients when determined one half hour following the injection

ANTIBIOTICS

Moldavsky Hasselbrook and Cateno (444) reported in 1945 that there is a marked shortening of the coagulation time of the blood following the parenteral administration of penicillin Macht and Ostro (445) reported that they had confirmed this observation on experimental animals and on man They stated that the intramuscular or intravenous injection of from 2 000 to 5 000 Oxford units of penicillin into a rabbit or a cat produced a difinite shortening of the coagulation time within 2 to 3 hours In 2 hemophilic human subjects the intramuscular injection of 50 000 to 75 000 units of penicillin did not hasten coagulation

Macht (446) tested amorphous penicillin the crystalline sodium salts of penicillin the isolated crystalline penicillin principles and streptomycin on animals and man Clotting times were de termined by the Lee White method Amorphous penicillin of every brand examined administered parenterally or by stomach tube mixed with amphojel markedly accelerated the clotting time Following injection an effect was noted within 15 to 30 minutes was most marked after an hour and persisted for several hours The sodium salt of crystalline penicillin produced a much less striking result Of the 4 crystalline penicillin principles X pro duced the most marked effect followed by K G and F A small amount of penicillin X added to penicillin G produced a syner gistic effect Streptomycin showed a marked thromboplastic effect on the blood of rabbits and cats When rabbits were used re

(4) Cysteine hydrochloride is well tolerated by most patients in doses up to 3 grams per day over many months

(5) It is suggested as an anticoagulant of rather low efficiency for use over long periods of time for conditions in which such an agent might be valuable

De Takats (457) studied the effect of sulphur compounds by means of the heparin tolerance test In every instance the injection of a single dose of 0 6 gram of sodium tetrathionate intravenously increased heparin sensitivity irrespective of the patient s previous type of reaction When sodium tetrathionate was injected intravenously in this dosage twice a week for 6 weeks there was improvement in the heparin tolerance as early as the 3rd day of treatment The response to heparin was increased markedly in all instances Given without heparin sodium tetrathionate did not prolong the capillary coagulation time When single doses of 1 gram of cysteine were given by mouth and the heparin tolerance curve determined between 15 and 120 minutes thereafter no effect was obtained nor were clear cut effects on the heparin tolerance noted in patients to whom 1 gram of cysteine was administered orally 3 times a day after meals for as long as 2 weeks

De Takats also mentions that patients receiving sulphonamide drugs have shown a remarkable response to heparin He concludes that sodium tetrathionate was found to increase definitely the patient s response to heparin after both single and repeated doses and that the use of this drug for the prevention of postoperative thrombosis and for the acute stages of Buerger s disease in which the heparin tolerance is poor is definitely worth while This has not been confirmed clinically

The importance of certain sulphur containing dietary factors and their normal metabolism in the prevention of hemorrhagic states within the body is probably considerably greater than is generally appreciated The role of sulphur containing products of incomplete protein metabolism in producing the clotting deficiency associated with obstructive jaundice has been discussed in detail by Carr and his associates (453 458) More recently Gyorgy (459) has summarized experimental observations of the hemorrhagic manifestations of certain dietary deficiencies including choline and cystine

mycin is added to oxalated diluted plasma the plasma will clot in a few minutes without the addition of calcium ions and thromboplastin The presence of prothrombin seems to be necessary for this clotting action of streptomycin

SULPHUR CONTAINING COMPOUNDS

Mueller and Sturgis (452) observed that cysteine hydrochloride inhibits the coagulation of whole blood in vitro and this work was confirmed and elaborated by *Carr and Foote* (453) who suggested that the delay in coagulation might be due to changes which they observed in the physical state of the fibrinogen Kuhnau and Morgenstern (454) also described inhibition of coagulation by glutathione within a certain range of pH

Sterner and Medes (455) found that cysteine and methionine ingested and injected intravenously in amounts varying from 1 to 3 5 grams prolong the bleeding time and the coagulation time in human subjects In vitro molar concentrations of cysteine from 0 16 to 0 64 markedly prolonged the coagulation time Methionine taurine and taurocholic acid exhibited somewhat similar properties They concluded that cysteine acted as an anti prothrombin

Hoefer Putnam and Gray (456) in experiments on the production of encephalitic lesions by the intravenous injection of coagulants found that cysteine hydrochloride given intravenously or by mouth prevented death from several times the usual lethal dose of a well standardized lung extract *Putnam and Hoefer* (205) then performed further studies which they summarize as follows

(1) The intracardiac injection of cysteine hydrochloride in dogs was followed by a prolongation of the coagulation time of 40 to 100 per cent in 3 out of 5 experiments

(2) The administration of cysteine hydrochloride to dogs by stomach tube was followed by an increase of clotting time of from 25 to 100 per cent in all technically satisfactory experiments

(3) Cysteine hydrochloride was also administered by mouth to 23 patients in whom the diagnosis of multiple sclerosis had been made In 17 a prolongation of the coagulation time was observed which varied from 30 to 90 per cent

slight shortening of the coagulation time was noted in the control dogs anesthetized with sodium pentabarbital although no such shortening occurred in dogs anesthetized with Dial

Levy and Conley (464) found that spinal anesthesia with procaine has no influence on the prothrombin clotting time They state that morphine shortens both the coagulation time and the prothrombin time Poindexter and Meyers found no change in the prothrombin clotting time of patients one half hour after the subcutaneous administration of morphine sulfate in doses of one quarter and one half grain

ADRENALIN (SYMPATHETIC PARASYMPATHETIC RELATIONSHIP)

Vosburg and Richards (472) first observed the accelerated coagulation of blood withdrawn from animals to whom adrenalin had been administered Cannon and his associates (465 473 474) reported that adrenalin in small doses intravenously and in larger doses subcutaneously would hasten the coagulation of the blood The same effect could be produced by stimulation of the splanchnic nerves by pain or excitement in the intact animal Since this effect did not follow these various stimuli when the liver and intestines were removed from the circulation they concluded that the common mechanism must be the action of adrenalin on the liver (and intestines?) Grabfield (475) confirmed the fact that very small amounts of adrenalin intravenously decreased the coagulation time but he ascribed the effect to a decrease in the amount of prothrombin in the blood

De Takats (476) interested in the relationship between sympathetic parasympathetic balance and the tendency to thrombosis studied the effect of epinephrine and of parasympathetic stimulants on patients by means of his heparin tolerance test He mentions that vagal stimulation has been reported to prolong the coagulation time by Plattner and Kodera (477) and by Zunz and La Barre (478 479) De Takats administered 0 001 mg of epinephrine intravenously to 2 hypertensive patients and found that the drug markedly inhibited the reaction to heparin The administration of 10 mg of mecholyl or of 1 cc of prostigmine 1 2000 subcutaneously to other patients elevated their heparin tolerance curves

Thyroid

Wakim Chen and Gatch (160) have demonstrated that the administration of desiccated thyroid alone has no significant influence on the prothrombin clotting time of the dog or the rat nor does the administration of desiccated thyroid have any significant influence upon the hypoprothrombinemic effect of dicumarol on these animals Shapiro (161) has confirmed this observation in man by administering from 0 1 to 1 0 gram (1 5 to 15 grains) of thyroid globulin (Proloid) daily to 16 patients for from 10 to 104 days In no instance was there a prolongation of the prothrombin clotting time of the whole or 12 5 per cent diluted plasma

Anesthetics and Hypnotics

Allen and Livingstone (162 163) observed that except in biliary tract surgery the prothrombin level of the blood did not fall post operatively when a variety of anesthetic agents were employed Their experimental studies on dogs confirmed the lack of effect of a variety of anesthetic agents on the prothrombin clotting time Following chloroform anesthesia there was however a reduction in prothrombin values Levy and Conroy (464) using the Smith bedside method for determining the prothrombin clotting time reported that ether anesthesia in the surgical stage shortens markedly the prothrombin time of the blood This method is however unreliable in most hands

Cannon (465) Uvnas (466) and Searles (467 468) have all reported that the coagulation time of the whole blood is shortened by ether anesthesia Searles found it to be unaffected by chloroform anesthesia

Fitzgerald and Webster (469 and Levy 470) have reported that the prothrombin clotting time is prolonged by sodium pentabarbital However Poindexter and Meyers (418) observed no significant change in the prothrombin times of 10 patients one half hour after the subcutaneous injection of 0 13 gram of sodium phenobarbital

Ellis and Barlow (471) reported that the coagulation time in cats and pigeons is decreased by barbital anesthesia Ramsey Pinschmidt and Haag (85) state in their studies on digitalis that a

SECTION IX

MISCELLANEOUS OBSERVATIONS

De Takats concluded that the clotting mechanism of patients as tested by their response to heparin is under neurogenic influence Adrenergic stimuli increase cholinergic stimuli decrease the tendency to thrombosis Fear apprehension nervous strain and hemorrhage increase the tendency to clotting prostigmine by its cholinergic action lessens the tendency to thrombosis Moses (442) however reported that the administration of 1 mg of epinephrine intravenously caused no significant or consistent change in the heparin tolerance curves of 5 subjects receiving 15 mg of heparin per kg *of body weight*

Link (37) stated that adrenalin could hasten the restoration of the prothrombin time when given to animals about to bleed from excessive doses of dicumarol This statement is supported by the work of Cannon and of Grabfield and by the report of Uvnas (466) that adrenalin stimulates the production of prothrombin by the liver

Wakim Fink and Chen (480) however using the Pohle and Stewart modification of the one stage method on 12 5 per cent diluted plasma were unable to demonstrate any significant change in the prothrombin clotting time of normal dogs and albino rats following the injection of adrenalin In dogs made hypoprothrombinemic by dicumarol the effects of adrenalin were variable and inconsistent and were therefore considered probably insignificant

CHAPTER 21

Heparinemia, or Hyperheparinemia

As POINTED out by Tocantins (481) there is some doubt that heparin is a component of normal blood or that it is the physiologic anticoagulant of the circulation Jaques and Waters (482) were unable to recover any heparin from as much as 4 liters of blood obtained from normal dogs Although protamine combines with heparin quantitatively the smallest amount of protamine which can be added to normal blood and still produce an effect usually delays rather than accelerates coagulation The same is true for toluidine blue and similar heparin bindings dyes Heparin in very minute concentrations actually accelerates coagulation

The concentration of heparin in the blood of man or the intact experimental animal is unknown No heparin or other anticoagulant has been found to date in any plasma fraction obtained by the method of Cohn Apparently a powerful cytolytic action is required to release heparin from the mast cells Even the blood of dogs with mast cell tumors which contain concentrations of heparin up to 50 times that found in extracts from liver contains no heparin and displays no alteration in coagulability from normal

However in animals heparinemia has been observed after the intravenous injection of peptone (483) ascaris extracts and trypsin (484) in anaphylactic shock (482 485) and after the exposure of the body to massive doses of ionizing radiation (486 487) More recently it has been reported that a heparin like anticoagulant is found in the blood of patients treated with one of the nitrogen mustards (488)

There is some evidence that heparinemia exists during the hemorrhagic phases of acute leukemia thrombopenias and aplastic anemias (321) In contrast to the experimental heparinemias which follow irradiation there is no direct evidence that heparin

anticoagulant Capillary dilatation leads to hemostasis edema and anoxia setting up a vicious cycle comparable to that encountered in irreversible shock (496) Once tissue anoxia is produced the cycle becomes more and more difficult to break Anemia is produced not only by loss of blood into the tissues and hollow viscera but by destruction of the erythropoietic tissues in the bone marrow and by increased phagocytosis of the erythrocytes

A titratable heparin like anticoagulant has been reported in the blood of irradiated animals (487 497 498) and the blood of irradiated animals is incoagulable in a test tube (497) However clotted blood and fibrin are present in the tissues of the same animals The coexistence of a circulating anticoagulant of a prolonged coagulation time in vitro and of the ability to form fibrin in vivo simultaneously is not explained as yet

is present in the blood of the patients with these conditions Therapeutic trials with protamine and toluidine blue have been made with inconclusive results Heparinemia may exist in clinical states accompanied by widespread tissue necrosis Anticoagulants other than heparin may be introduced into the blood or if already present may be increased in amount (189 190)

The view that an absolute deficiency of platelets of prothrombin or of fibrinogen is necessary for diminished coagulability of the blood may have to be modified in the light of facts recently accumulated

The Effect of Ionizing Radiation Upon the Blood

Tullis (491) has reported a comparative study of the lesions produced in swine after total body exposure to ionizing radiations from the atomic bomb tests at Bikini and after total body exposure to million volt irradiation The lesions produced by the 2 types of exposure were found to be indistinguishable and to consist mainly of

(1) Hemorrhage
(2) Necrosis and
(3) Secondary infection

It is emphasized that when ionization is produced within the tissues the biological effects of any of the several types of ionizing radiation are essentially similar (192 195) The effect produced by penetrating external radiations is similar to the effect of materials deposited internally provided that equal amounts of roentgen units or equivalents are delivered to the tissues

Hemorrhages occur as petechiae ecchymoses and sometimes as hematomata involving all parts of the body and all types of tissue There is extravasation of blood into tissue spaces throughout the body accounting for considerable blood loss but a much more voluminous blood loss occurs via the gastrointestinal and urinary tracts Surface erosions and ulcerations in the gastrointestinal tract bleed grossly No ulcerations are seen grossly in the kidney pelves to account for the considerable blood loss from this source Clinical hematuria is a sign of severe radiation illness

The generalized hemorrhage is caused by increased capillary permeability aided perhaps by the presence of a circulating

sedimentation rate determined before the administration of heparin and 30 minutes and in some instances 90 to 300 minutes after the injection of heparin Amounts of heparin which prolonged the venous clotting time to between 50 and 220 minutes did not increase or decrease the erythrocyte sedimentation rate significantly

Dicumarol was administered orally in amounts aimed to maintain a therapeutic prolongation of the prothrombin clotting time This dosage was usually 300 mg the 1st day 200 mg the 2nd day and amounts determined by the daily prothrombin time thereafter The sedimentation rate and the prothrombin clotting time were determined prior to the administration of dicumarol and at intervals of from 1 to 3 days during and subsequent to dicumarol therapy The sedimentation rate was not altered significantly during dicumarol therapy

Because Walker and Rhoads (291) had reported that the effect of heparin was augmented by the concurrent administration of dicumarol the effect of combined heparin and dicumarol therapy administration was studied on 5 individuals When dicumarol was given in doses sufficient to produce a marked hypoprothrombinemia there was no effect on the erythrocyte sedimentation rate and when heparin was given in addition to dicumarol in amount sufficient to prolong the venous clotting time there was still no alteration in the erythrocyte sedimentation rate

CHAPTER 22

The Effect of Anticoagulants on the Erythrocyte Sedimentation Rate

SINCE heparin and dicumarol in ordinary therapeutic doses do not alter the erythrocyte sedimentation rate of the patient receiving anticoagulant therapy the erythrocyte sedimentation rate of such patients may be utilized as a guide to diagnosis and prognosis in exactly the same manner as it is in patients not receiving anticoagulant therapy

The sedimentation rate of heparinized blood has received considerable attention because heparin has been used in vitro as the anticoagulant for samples of blood obtained for the purpose of determining the erythrocyte sedimentation rate Although earlier reports were conflicting they supported in general the view that *the sedimentation rate of heparinized blood is somewhat more* rapid than that of citrated or oxalated blood (499 505) It was noted also that heparin in unusually high concentrations produces an accelerated sedimentation rate (503 506) Finally it has been observed repeatedly that there is a rapid separation of the plasma and cells of heparinized blood placed in test tubes for the determination of the venous clotting time (170 288)

Although Wright and Prandoni (42) reported in 1942 that dicumarol does not increase the sedimentation rate several subsequent reports have held the opposing view (40 211 507) It is of interest in this connection that the group at the Mayo Clinic has reversed its original stand and now agrees that dicumarol does not accelerate the erythrocyte sedimentation rate (508)

Cosgriff (509) has recently reported a well-controlled study on blood specimens from patients receiving therapeutic amounts of dicumarol heparin or combined anticoagulant therapy The sedimentation rates were determined by the Westergren method Heparin was administered intravenously in intermittent doses of 50 mg to 10 subjects and the venous clotting time and erythrocyte

12 patients exhibited no clinical or electrocardiographic evidence of cardiovascular disease 16 were patients with cardiovascular disease and abnormal electrocardiographic patterns 14 were patients with acute infarction and 6 patients were digitalized The effect of dicumarol administration was closely controlled by daily determinations of prothrombin activity and microscopic examination of the urine for hematuria Leads I II III CF_2 and CF_4 and CF_5 were taken and electrocardiographs were thoroughly analyzed No electrocardiographic effects of hypoprothrombinemia were shown by subjects on maximal doses of dicumarol with depression of prothrombin activity to less than 10 per cent of normal In general no significant electrocardiographic deviation attributable to dicumarol was observed

CHAPTER 23

The Effect of Anticoagulants on the Electrocardiogram

THE administration of either heparin or dicumarol to a patient has no direct influence on the electrocardiogram There is both experimental and clinical proof of this fact in the instance of dicumarol We are not however aware of any studies on this point in connection with heparin

In their studies on the use of dicumarol in experimental coronary occlusion in dogs in which the descending branch of the left coronary artery was ligated Beattie Cutler Fanteaux Kinney and Levine (162) studied the evolution of the electrocardiographic changes in the control animals and in those to whom dicumarol was administered Electrocardiograms were taken immediately postoperatively daily for 1 week postoperatively and on the 14th postoperative day just prior to the sacrifice of the animals Electrocardiographic changes in all animals irrespective of whether they received anticoagulants or not included singly or in combination displacements of the RS T segments changes in the direction of the T waves ectopic rhythms and conduction disturbances typical of those described in similar ligation experiments in the literature No fewer instances nor lesser degrees of these changes developed in the dicumarol treated than in the untreated animals The authors conclude that there are no significant differ*ences in the electrocardiographic findings between the 2 groups*

The same conclusion was reached by LeRoy and Nalefski (163) in similar experiments in which anterior infarction was produced by ligation of the descending branch of the left coronary artery of dogs Serial electrocardiograms showed no variation in the rate or the character of the evolution of changes in dogs treated with dicumarol as compared to untreated control animals

Balkin and Gootnick (510) have investigated the effect of dicumarol on the electrocardiogram in a series of 48 patients Of these

SECTION X

RFCENT DI VELOPMENTS

IN A FIELD so dynamic developments during the period re quired for the publication of a monograph are often of funda mental importance and may in fact alter certain basic concepts held at the time of writing For this reason it was planned to append a final section written immediately prior to printing and designed to present the most recent advances

The number of articles published during the past year has been formidable and it has been impossible to assess the ultimate value of many For this reason the material is presented largely in the form of abstracts without personal comments For convenience in relating the material which follows to subject matter which has been presented in the preceding sections this final section has been divided into nine chapters Each of these chapters is con cerned in general with the same subjects referred to in a single section of the preceding text The list of references while com prehensive does not pretend to include every article published during the past year Some older references of particular interest which were overlooked in the writing of the original manuscript are included in the following pages

C D M
I S W

CHAPTER 24

Thromboembolic Phenomena in Clinical Medicine

Venous Thrombosis

According to Stanton (511) varicose dilatations in the deep veins of the lower extremities are important in the development of thromboembolic disease in man Data from 50 venographies and 6 anatomical dissections suggested that (1) the deep venous system of the lower extremity tends to have a greater cross section in older than in younger individuals (2) in persons over the age of 40 local saccular dilatations not uncommonly occur in the deep veins of the calf (3) such local lesions are commonly situated proximal to the valves where hydrostatic pressure is probably greatest in the erect position and are accompanied by histological changes in the vessel wall and (4) slowing and puddling of injected contrast media occurs in these dilated areas in vivo

Pulmonary Embolism

The necessity of making the diagnosis of venous thrombosis early if pulmonary embolism is to be prevented is emphasized by recent articles of which the following are good examples

Evoy (512) surveyed 1 000 proven cases of pulmonary embolism from 6 reports in the literature and including 130 cases previously unreported The choice of material depended mainly upon the completeness of reporting and upon the presentation of statistics in a reasonably similar manner Among 172 patients known to be suffering from medical illnesses there was a preponderance of cardiovascular diseases (81 patients) and a significant number of malignancies (35 patients)

Among 111 patients who developed a fatal pulmonary embolus postoperatively the peak incidence was on the 7th postoperative day and a second lower peak was reached on the 13th day The average time for the occurrence of fatal pulmonary embolism was

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12 5 days following operation Sixty per cent of fatal pulmonary emboli occurred by the 7th day and 80 per cent by the 14th day

In Evoy s own series hemoptysis occurred in 13 patients or 10 per cent of 130 cases Clinical evidence of phlebitis was recognized in only 18 patients or 15 5 per cent of 116 cases of these 15 or 78 9 per cent had one or more infarcts at autopsy Activity most commonly straining at stool was associated with the release of a fatal embolus in 20 or 15 4 per cent of 130 patients Symptoms of prelethal emboli had occurred in 37 or 31 8 per cent of 116 patients Since 50 4 per cent of these cases exhibited one or more infarcts at autopsy 18 6 per cent of patients had suffered asymptomatic infarcts

Among 246 patients in two series 69 per cent died within one hour and 92 per cent within 24 hours following recognized pulmonary embolism In Evoy s own series half of the patients with fatal pulmonary embolism died within one hour and 92 per cent within 24 hours

Among 216 patients from combined series 60 7 per cent had one or more pulmonary infarcts at *autopsy* In the author s series 58 or 50 4 per cent of 115 patients had one or more infarcts and 34 8 per cent had multiple infarcts The position of individual infarcts in 78 cases in two series was preponderantly in the lower lobes 38 4 per cent on the left and 42 3 per cent on the right Probable sources of emboli were found in 463 or 77 per cent of 601 patients Nearly 80 per cent were from the leg veins and about 15 per cent from the heart

Zimmerman Miller and Marshall (513) found pulmonary emboli in 6 1 per cent of 5 588 autopsies Emboli in 166 autopsies were purely *incidental findings* originating in bland thrombi in 154 instances and from infective phlebitides in 12 instances *Pulmonary emboli which contributed to the patient s death* occurred in 108 instances from bland thrombi in five instances from non suppurative thrombophlebitis and in 10 instances from suppurative phlebitis Massive fatal pulmonary embolism resulted from bland thrombi in 53 instances and three also occurred in patients with non suppurative thrombophlebitis Emboli which had produced death clinically were found in 1 per cent of all autopsies

Incidental emboli arose mainly from small mural thrombi in

auricular appendages in patients with cardiac decompensation or auricular fibrillation or from the ventricular walls and sites of myocardial infarction The most frequent sites of origin of emboli which contributed to or caused death were the veins of the lower extremities Most incidental emboli occurred in medical patients but fatal emboli were three times as frequent in surgical as in medical patients and constituted the primary cause of death in 0 05 per cent of patients undergoing major surgery

In the less severe forms of pulmonary embolism cardiac disease was the most important predisposing factor in fatal embolism debility and impaired general health were the most important pre disposing factors Phlebothrombosis or thrombophlebitis were rec ognized clinically before fatal embolism in only 7 patients Pre monitory non fatal emboli occurred in 14 patients but fatal emboli occurred in 12 without warning

The authors advise venous ligation in instances of phlebothrom bosis and anticoagulant therapy in thrombophlebitis Exercise and motion are encouraged and the patient is made ambulatory with the support of an elastic bandage as soon as the temperature has become normal Our own experience warrants the use of anti coagulant therapy in cases of both types

According to Dehlinger and Riemenschneider (511) there was no significant decrease in the percentage of cases in which pul monary emboli were demonstrated at necropsy at the New England Deaconess and New England Baptist Hospitals since the introduc tion of definitive and prophylactic treatment of venous thrombosis This therapy included venous ligation the administration of the anticoagulants prophylactic exercises early ambulation and para vertebral sympathetic block in 1 case

During the 13 years from 1928 through 1940 pulmonary emboli were found in 7 5 per cent of all autopsies during the following 6 year period in 6 7 per cent The percentage of operations fol lowed by pulmonary embolism as determined at autopsy de creased from 0 13 per cent to 0 09 per cent a decrease that is not definitely significant statistically

The authors sought to explain why many patients are still dying of pulmonary embolism despite the availability of anticoagulant drugs and the use of venous ligation No analysis was made of the

numerous successfully treated cases Hence this report is an indication that the problem of preventing pulmonary embolism is still great and not a condemnation of the methods used at the present time

Seventy four cases in which necropsy was performed between 1941 and 1946 were analyzed according to age sex immediate cause of death primary site of thrombus medical versus surgical status and preventive therapy *In only five of the 74 cases of pulmonary emboli did the patient receive specific therapy for the prevention of embolism This supports the view that the primary problem is the difficulty in the early diagnosis of venous thrombosis and of non fatal pulmonary embolism* We have been increasingly impressed with the fact that inadequate treatment may be little better than no treatment

Vander Veer Kuo and Marshall (515) studied 204 cases of thromboembolic disease including 83 patients with pulmonary embolism during a two year period Seventy per cent of the patients were 40 years or older Nearly one half of the patients suffered from chronic medical illnesses

Of the 83 patients with pulmonary embolism 37 presented little or no evidence of venous thrombosis of the extremities and post mortem study revealed soft clots in the large veins of the pelvis and abdomen in three of these cases Five patients developed pulmonary embolism after bilateral femoral ligations and two of them died Five patients developed retrograde thrombosis of the femoral veins after embolism Patients suffering from pelvic fractures chronic heart disease and prostatic abdominal and pelvic operations were especially prone to develop pulmonary embolism

Anticoagulant therapy was given to 114 of the 204 patients One patient developed an attack of non fatal pulmonary embolism during the administration of heparin and one patient died Femoral ligations performed on 46 patients were followed by five instances of pulmonary embolization and three fatalities

BED-REST AND THROMBOEMBOLISM

The hazard of thromboembolism has been used as an argument against the application of strict bed rest to the treatment of tuberculosis Zahn and Peirce (516) reviewed 3 672 autopsies at Fitz

simons General Hospital of which 1 700 were on tuberculous subjects The uncorrected incidence of thromboembolism in the tuberculous group was 2 1 per cent and the corrected incidence was 1 5 per cent The authors state that this incidence is less than one fifth that reported in the literature for non tuberculous diseases In only three cases could the cause of death be ascribed to pulmonary embolism

It is suggested that in cardiac patients mural thrombi may be more important sources of emboli than are the peripheral venous channels The possible etiological factors in the production of thrombosis are discussed The authors conclude that thromboembolism does not constitute a significant threat to the life of the tuberculous patient who is being treated with strict bed rest

Cook and Lyons (517) observed 45 paralyzed veterans representing a total of 115 man years in which their lower extremities were not moved voluntarily They had been subjected to 175 operations There was not a single death from pulmonary embolism during the period of observation although the coagulation mechanism of these patients was often defective Factors producing venous injury and venous stasis in the lower extremities were reviewed by the authors who concluded that the young average age of these patients accounts for the low incidence of thromboembolism

The Dual Pulmonary Circulation and Pulmonary Infarction

Various observers have noted that an embolus to the lung may not produce pulmonary infarction in a person with a normal circulation Pulmonary embolism is rather commonly followed by pulmonary infarction in the presence of pulmonary congestion and edema This situation is generally explained by the presence of a dual circulation to the lungs through the bronchial and pulmonary arteries Westermark reported that only 20 per cent of instances of pulmonary embolism confirmed at necropsy showed evidence of infarction and concluded that hemorrhagic infarcts occur only when there is an occlusion of both the bronchial and pulmonary arteries

The role of the bronchial arteries has been studied by many investigators It has been demonstrated repeatedly that there is an independence of the bronchial and pulmonary arterial systems in

normal lungs except for capillary anastomoses (518 521) Such capillary anastomoses connect the bronchial arteries with the pulmonary arteries and with the pulmonary veins as well (522) Changes in the pulmonary arterial system are followed by changes in the bronchial arteries

Virchow (523) demonstrated that chronic obstruction to a branch of a pulmonary artery serving one lobe of the lung results in an increased bronchial arterial development and this work was confirmed by the *experimental studies of Mathes Holman and Reichert* (518) The development of a collateral circulation through the bronchial arteries in instances of pulmonary artery atresia and stenosis was demonstrated by Christeller (524)

Rather striking changes in the dual circulation in the lungs of individuals dying of various diseases were reported by Wood and Miller (525) These included the development of numerous bronchial pulmonary arterial anastomoses in the presence of cardiovascular diseases which result in an elevated pulmonary venous pressure and are possibly associated with lesions of the pulmonary vascular tree

Chapman Gugle and Wheeler (526) produced pulmonary embolism in 12 normal dogs by releasing from the jugular veins blood clots produced by the injection of thrombin Infarction was not demonstrable at autopsy three to 10 days later

Pulmonary congestion was produced consistently in four dogs given alpha naphthylthiourea intravenously When eight dogs were injected with alpha naphthylthiourea just before release of intravascular clots three showed pulmonary infarction distal to emboli and four showed intraalveolar hemorrhage without necrosis distal to the emboli

These results suggest that embolism alone does not produce infarction of the normal lung probably because of adequate collateral blood supply through the bronchial arteries or through anastomoses between the intralobar pulmonary arteries Interference with this circulation by congestion or edema is apparently necessary for pulmonary infarction

Shapiro and Rigler (527) reported three instances confirmed at autopsy of pulmonary embolism without infarction Ischemia of

the involved pulmonary segment was represented radiologically by a segmental area of increased radiability. The vascular pattern was well outlined central to the site of embolism, but stopped abruptly at the involved area. The local area with diminished or absent vascularization corresponded to the pulmonary segment supplied by the occluded vessel.

It is apparent that pulmonary embolism without infarction can be diagnosed radiologically. Segmental obstructive emphysema, localized non-obstructive emphysema, and pulmonary embolism without infarction produce an identical roentgen appearance, but can be differentiated often on clinical grounds.

THROMBOEMBOLISM IN CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION

Wang, Bland and White (528) found a total of 556 cases of myocardial infarction and 130 cases of coronary thrombosis without infarction among 7,028 consecutive autopsies performed at the Massachusetts General Hospital between 1926 and 1945, inclusive. Of the 556 cases of myocardial infarction, 267 were recent and 289 were old and healed. The anterior wall of the left ventricle was involved almost twice as often as the posterior wall. Lesions limited to the septum or to the right ventricle were infrequent, but extension into the septum by fresh anterior or posterior infarcts was not uncommon, occurring in 72 of 190 hearts with anterior and in 35 of 109 hearts with posterior infarction.

Large cardiac aneurysms due to infarction were found in 10 per cent of cases, although small shallow aneurysmal dilatations were common. Rupture of the ventricular wall at the site of infarction occurred in less than 5 per cent of cases. Both aneurysms and ruptures were preponderantly in the anterior wall of the left ventricle. There was a single ventricular spetal defect at the site of an infarct.

Of 207 patients with thrombi in the chambers of the left heart, 95 had peripheral emboli at autopsy. There were half again as many patients with a peripheral arterial occlusion who did not exhibit a thrombus in the left heart, suggesting that the embolus constituted the entire thrombus or that a local thrombus formed

in the artery Pulmonary embolism occurred in 106 cases and could not be related to intracardiac thrombosis in most instances Most often it was due to unrecognized thrombosis of a leg vein Pericarditis occurred in about one third of the acute and in about one quarter of the chronic cases, but was always slight in degree

CHAPTER 25

The Mechanisms of Intravascular Clotting

Prothrombin and Accelerator Factors

MOST workers agree that normal plasma contains an accelerator factor which affects the transformation of prothrombin to thrombin Such a factor has been described by various observers but there is not complete agreement as to the identity or non identity of these factors Since they have been discovered and studied under various experimental conditions and by different methods (Table XII) it is impossible to state categorically whether there is a single plasma accelerator substance or several

A J Quick denies the existence of an accelerator factor Quick and Stefanini (529) concluded that the formation of thrombin requires component A the labile factor thromboplastin and combined calcium They contend that the reaction follows the law of mass action

According to these authors component A (prothrombin) exists partly free and partly in an inactive or precursor state in fresh human plasma A rough surface is necessary for its activation but calcium thromboplastin and thrombin are not In oxalated human plasma nearly all component A is activated after 24 hours if kept in contact with a rough surface such as glass

In thromboplastin deficient plasma (in hemophilia or in platelet free plasma) coagulation is accompanied by a marked increase in the concentration of free component A because little of the active form is consumed and additional amounts are produced from the inactive precursor There are 2 types of congenital hypoprothrombinemia associated with a deficiency of component A (1) a deficiency of both free and total component A and (2) the more common hereditary form in which the total amount of component A is normal but the amount of free component A is reduced

Quick and Stefanini believe that the descriptions of prothrom

TABLE XII

PROTHROMBIN CONVERSION ACCELERATOR FACTORS DESCRIBED IN THE LITERATURE

Author(s)	Name Applied to Fact r	Author s Opin on As To Identity of Factor	Manner of Di covery of Factor
Fantl and N nce	Plasma Factor		First reported that the proth omb n time of plasm d l ted with prothrombin free pl sm is shorter than that of plasma dil ted to the s me deg ee w th sali e
Ow en P	Factor V (& F ctor VI)	Identical with Plasma F ctor of Fantl nd Na ce with Seeger s Ac globulin and w th Quick s L bile Factor	Studied a patient with a hem rh g c tendency whose clotti g times and p thrombin t me by the one stage method were prolonged b t whose pl sma w s shown to have a norm l prothrombin c ntent Mi te amounts of norm l pla m added to the patient s plasm vitr r st ed the p othrombin time to normal Ad mini t ation of norm l plasma to the patient temporarily c ected the coagulat on defect
Seege s et al	Ac glob lin (S um Ac globulin Plasma Ac globulin)	Identical w th Owre s F c tors V and VI but n t the s me as Q ck s Labil F c tor	Confi med the find gs of Fantl and Nance and of Ow n that an add tional factor is co rned n th c n version of prothrombin t thromb i Demonstr ted that th accel r tor fact ex sts n serum n a more ac tive fo m than in pl m
Quick A J	Compon nts A nd B Labil F ctor	Labile F ctor ident cal with Owren s F ct r V b t not w th Seeg Ac glob l n Quick st tes clearly th t the formation of thrombin fol lows the law of m ss ct on nd that the de c pt o s of accelerato ff cts re in real ity th ctivation of C mpo nent A	St d es on st ed pl sm and on pa tients w th d opathic hypop othrom binemia by the stage method of p thromb n d termi tion Con cl d d that p othrombin s a com plex of three c nponent C mpo n t A and B and the Labil F ctor
Honorato	Pl sm tic Cofa to f Thrombo pl st n	M y be id t c l with Qu k s Lab l F ctor	D g stud on the d orpt on of pr thr mbi by v o s salts s p rated a facto which is not prothrom b b t wh h a ists i the conve s n of prothromb n to thrombi
Alexander et l	S m P othromb n Conv sion Acc ler to (SPCA)	M y b Ow e s F ctor VI o S s A glob lin but is n t Quick Lab l F cto	Show d that when sm ll am nts of s rum dd d to pl sma there is m kedly r d ced p thromb n time by the one stage m thod t trib te l to the p s ce ser m f proth o bin co i n cele t facto

bin conversion accelerator factors represent the activation of component A They suggest that the two stage method does not distinguish between free and inactive forms of this component since the method depends upon the conversion of all prothrombin to thrombin

The use of amberlite which quantitatively removes calcium from the blood and other new technics have been utilized by Quick and Stefanini (530) to reinvestigate the role of ionized calcium in coagulation They conclude that sodium oxalate precipitates ionized calcium and also removes it from a compound which is essential for coagulation Citrate combines with and inactivates prothrombin The addition of magnesium or strontium restores the prothrombin to its original state Studies of prothrombin activity under various conditions suggest the presence of a labile factor which is indispensable to coagulation

Ac globulin

Lewis and Ferguson (531) studied the clotting time in vitro of blood to which had been added in varying amounts prothrombin serum Ac globulin tissue thromboplastin thrombin and fibrinogen They found that a thrombin yield is directly dependent on the concentration of calcium and that Ac globulin increases both the rate of formation and the yield of thrombin from a given amount of prothrombin thromboplastin and calcium Ac globulin is necessary for the formation of any thrombin Thromboplastin exerted effects similar to those of calcium and Ac globulin Without tissue thromboplastin no thrombin is formed It was concluded that the thrombin yield as well as its rate of formation depends upon the quantity of each of the four agents—prothrombin serum Ac globulin thromboplastin and calcium

Seegers and Ware (532) reviewed recent advances in the knowledge of prothrombin and the role of the accelerator factor They stated tentatively that the labile factor (Quick) the plasmatic cofactor (Honorato) the prothrombin convertability factor (Smith) factor V (Owren) Ac globulin (Ware Guest and Seegers) and the accelerator factor (Fantl and Nance) are one and the same substance

Seegers and Ware criticize the one stage method of determining

prothrombin as vagarious, but admit that while it does not measure prothrombin concentration it is a useful tool for measuring the total coagulability of the blood The two stage method has been modified so that it measures the actual prothrombin concentration and it can be used to accurately determine Ac globulin quantitatively The authors believe that the two stage method should be used more commonly once the reagents are available commercially since the procedure is not difficult to perform

Fahey Ware and Seegers (533) studied the stability of the plasma accelerator substance known as Ac globulin and of prothrombin under specific conditions Human venous blood was drawn into citrate or oxalate mixtures and then after various manipulations (centrifugation at various speeds storage for various lengths of time use of various concentrations of oxalate or citrate) tested for prothrombin and Ac globulin contents

Ac globulin was determined by a method in which prothrombin thromboplastin and calcium are present in controlled amounts so that the rate of formation of thrombin measures the amount of Ac globulin The amount of prothrombin was determined (1) by a standard two stage procedure in which saline is the diluent and (2) by a modified two stage procedure in which bovine serum (containing Ac globulin) is the diluent

In both oxalated and citrated plasma the prothrombin activity remained constant for several days and then fell progressively when studied by the standard two stage method By the modified method in which Ac globulin was added the amount of prothrombin remained unchanged for as long as 56 days The conclusion is that the decrease in prothrombin is actually due to the loss of Ac globulin and not prothrombin itself from the plasma

When a sample of oxalated plasma which originally had a prothrombin content of 290 units per cc was stored for 53 days the prothrombin content by the standard two stage method was 19 units per cc When the determination was modified by the addition of (a) bovine serum (b) pure Ac globulin or (c) an extract of bovine platelets the prothrombin content after 53 days was found still to be 290 units per cc Not only serum but platelets as well contain a prothrombin accelerator factor Platelets were

also shown to contain a factor which decreases the stability of Ac globulin

The authors conclude that plasma serum and platelet Ac globulin substances are similar that they are the same as Quick s prothrombin A and Owren s Factor V and that they are important factors in the initial stage of coagulation

Murphy and Seegers (534) determined the concentrations of pro thrombin and Ac globulin in the blood of various animals in cluding man and noted a wide variation between species The dog man and the guinea pig have identical prothrombin con tents according to the two stage method but widely divergent pro thrombin times by the one stage method This is due to wide dif ferences in the Ac globulin concentrations in these species Man has a low Ac globulin activity and therefore a relatively high ratio of prothrombin to Ac globulin This suggests that there may be a relatively narrow margin of safety beyond which hypopro thrombinemia may occur

Fahey Ware and Seegers (535) found that the prothrombin content of plasma obtained from blood which contains 0 0087 M sodium citrate remains constant for at least 21 days when stored at 5° C Under the same conditions the Ac globulin content re mains constant for a week and then gradually decreases to 55 per cent in two weeks and to 30 per cent in three weeks Ac globulin appeared to be somewhat less stable in whole blood than in centri fuged blood Hence for the reliable estimation of prothrombin by the two stage method it is necessary to add Ac globulin if it is not already present in the blood sample in sufficient quantities

Analysis of extracts of bovine platelets by Ware Fahey and Seegers (536) altered the concept that platelets initiate coagulation by the liberation of thromboplastin Actually only minute amounts of thromboplastin were found in platelets In addition two other substances were present (1) an Ac globulin substance and (2) a new factor called platelet factor 2

Platelet extracts were found to contain a substance which acted similarly to Ac globulin in accelerating the conversion of pro thrombin to thrombin in the presence of thromboplastin and cal cium It was quantitatively identical with serum Ac globulin in

its ability to convert prothrombin to thrombin Platelet Ac globulin and serum Ac globulin were both similarly precipitated by half saturated ammonium sulfate Both were destroyed by heating to 53° C but there was a difference in their length of stability at this temperature Only platelet Ac globulin could be sedimented in the ultracentrifuge It was concluded that platelet Ac globulin and serum Ac globulin are probably two different proteins which have similar prothrombin activating properties

Platelet extracts were found to possess a previously undescribed property that of hastening the action of thrombin on fibrinogen This effect was diluted out rapidly

It is emphasized that neither serum nor platelet Ac globulin are absolutely necessary for the production of thrombin but act merely as catalysts

Serum Prothrombin Conversion Accelerator

Alexander and his coworkers at Beth Israel Hospital in Boston have published a series of papers during the past year describing results of studies on coagulation These include a description of a prothrombin conversion accelerator factor (SPCA) and a new theory of blood coagulation based upon the existence of this accelerator factor

Alexander and de Vries (537) reported that the prothrombin activity of stored plasma as determined by the one stage technic can be fully restored by the admixture of any one of the following barium sulfate plasma (prothrombin free) congenital afibrinogenemic plasma hemophilic plasma or fresh normal plasma The restorative factor (labile factor) is not fibrinogen

Prothrombin free plasma (barium sulfate) has a normal amount of labile factor fibrinogen and antihemophilic activity Its use as a diluent in measuring prothrombin by the one stage technic is advantageous since the non prothrombin variables are adequately controlled Plasma stored for more than 2 weeks shows enhanced prothrombin activity when measured by the barium sulfate plasma dilution method

According to Alexander Landwehr and Goldstein (538) serum contains a substance which arising during coagulation can accelerate the conversion of prothrombin to thrombin Many of the

properties of this factor (SPCA) have been determined and it has been separated in a fraction of serum comprising 20 mg of protein per 100 cc of serum (539 540) Evidence presented by Alexander and his associates indicates that SPCA is a new clotting factor distinct from the Ac globulin of Ware and Seegers factors V and VI of Owren and the labile factor of Quick (541 542 543)

The amount of accelerator which evolves during coagulation is related to the amount of prothrombin consumed In hypoprothrombinemia whether congenital dicumarol induced or resulting from liver disease abnormally small amounts of accelerator are elaborated The interaction of purified prothrombin preparations with thromboplastin and calcium yields substantial amounts of SPCA in addition to thrombin Alexander proposes that prothrombin may be split during its conversion to give thrombin and SPCA This concept is supported by certain remarkable similarities between prothrombin and the accelerator

SPCA cannot accelerate the conversion of prothrombin in the absence of a labile factor in plasma which Alexander believes is identical with Quick s labile factor Owren s factor V and the plasma Ac globulin of Seeger On this basis Alexander Landwehr and Goldstein propose a new theory of coagulation as follows

> In the presence of thromboplastin and ionized calcium prothrombin is split slowly into thrombin and SPCA Under the influence of this SPCA plasma Ac globulin is converted into serum Ac globulin which then accelerates the conversion of additional prothrombin to thrombin and more SPCA The reaction proceeds with increasing velocity until prothrombin is almost entirely consumed

The authors conclude that a reduction in serum accelerator rather than hypoprothrombinemia per se may explain the efficacy of dicumarol in preventing and treating thromboembolic diseases

Jacox and Bays (544) found that in individuals with a normal quantity of plasma prothrombin the rate of disappearance (or degradation) of the serum prothrombin converting factor is constant but that in sera from individuals receiving dicumarol the degradation rate of the serum prothrombin converting factor

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24 hours Fibrinolysis occurred even before operation in anxious patients and could be produced by exercise suggesting that its initiation might be associated with the release of epinephrine although epinephrine does not produce fibrinolysis in vitro Judging from the effects of injection of epinephrine in certain pathological states fibrinolysis is independent of the functions of the adrenal cortex the spleen pancreas and liver but may involve lymphoid tissue

Plasmin is thought to participate in the reabsorption of fibrin formed in all inflammations in the disintegration of thrombi and in the dissolution of endometrial clots during menstruation In chloroform poisoning there is a demonstrable fall in serum fibrinogen It is postulated that plasmin functions as one of the enzymes necessary for the conversion of prothrombin precursors to their more active forms in blood coagulation Plasmin may be responsible for the lowering of serum albumin in Selye s alarm reaction and may be associated with the release of histamine in anaphylaxis

The finding of fluid and incoagulable blood at autopsy is not uncommon A study was undertaken by Mole (547) to explain this phenomenon Blood was obtained from the heart and great vessels of 61 cadavers at routine but not consecutive autopsies Observations were made on the fibrinolysin in supernatant serum by a modification of Macfarlane s method Cadaver fibrinolysin appears to be a globulin It is non dialyzable is precipitated at neutral pH in 50 per cent saturation of ammonium sulfate and is inactivated by pepsin The appearance of fibrinolysin seems to be part of the body s general reaction to injury and it is probably produced by the endothelium

Guest Daly Ware and Seegers (548) assayed in human patients the plasma antifibrinolysin which inactivates bovine fibrinolysin Antifibrinolysin activity was increased in pernicious anemia pneumonia intestinal obstruction acute bacterial endocarditis cirrhosis of the liver and coronary thrombosis Single patients with hemophilia and with hemorrhagic purpura showed no change in plasma antifibrinolysin activity Plasmas of patients exhibiting no obvious pathology were relatively uniform in antifibrinolysin activity

usually varies directly with plasma prothrombin concentration Sera and plasmas from patients receiving dicumarol were assayed daily for prothrombin by one and two stage technics and the serum prothrombin converting factor degradation rate determined There was a good correlation between the two determinations although the measurement of the degradation rate of serum prothrombin converting factor was no substitute for conventional methods of prothrombin assay

Miale (545) attempted to define the relationship of staphylocoagulase to blood coagulation Sterile cell free filtrates of broth *cultures of some strains of staphylococci contain staphylocoagulase* which clots oxalated plasma but not purified fibrinogen When a plasma factor (coagulase globulin) is added to staphylocoagulase a thrombin like substance (coagulase thrombin) is formed which is able to clot purified fibrinogen When the clotting times of plasma containing increasing amounts of either staphylocoagulase or coagulase thrombin are plotted against concentrations of the clotting agents hyperbolic curves are obtained which are similar to those obtained with prothrombin or thrombin Miale states that coagulase globulin appears to be distinct from Ac globulin the V factor of Owren and the anti hemophilic globulin of Taylor et al The substance could not be demonstrated in platelets

Fibrinolysin

Macfarlane and Biggs (546) have reviewed the process of fibrinolysis and have correlated current concepts with their own observations The proteolytic enzyme of the plasma is called plasmin (*serum trypsin serum protease serum tryptase fibrinolysin thrombolysin*) and its inactive precursor is termed plasminogen The streptococcic filtrate factor is called streptokinase and the antibody developed by patients recovering from streptococcic infection antistreptokinase The inhibitor of plasmin found in plasma is called antiplasmin

Since traumatic shock had existed in all cases in which fibrinolysis had been demonstrated Macfarlane investigated the blood of patients undergoing surgical operations A fibrin web in normal blood samples was found to remain for weeks but fibrin webs in blood removed from patients recently operated disappeared in

suggesting that thrombocytopenic purpura is accompanied by a serious coagulation defect which has hitherto been unrecognized because it is masked by a normal coagulation time

Conley Hartman and Morse (554) prepared human platelet free plasma by use of silicone treated apparatus and high speed centrifugation and determined its clotting behavior Needles syringes test tubes and pipettes were treated with silicone after the method described by Jaques A multiple syringe technic was used and the contents of the first syringe were discarded Thirty to 40 cc of blood in treated tubes were centrifuged at 7 000 r p m at 4° C for five minutes to remove cells and most of the platelets The upper portion of the plasma was removed with a silicone treated pipette and recentrifuged at 12 000 to 14 000 r p m for 10 minutes Thereafter the upper layer of this plasma was removed and stored in silicone treated tubes in an ice bath Normal plasma obtained in this manner remains fluid for at least several days at 4° C It was not always possible to obtain plasma entirely free of platelets but platelets appeared to be completely absent in some instances

Of the 86 subjects studied 41 were normal persons and the others had various diseases Normal platelet free plasma clotted in a relatively short time in glass tubes at 37° C but its clotting time in silicone treated tubes was greatly prolonged and sometimes clotting did not occur This observation suggests that contact with glass activates some plasma constituent which can initiate clotting This factor is apparently activated slowly or not at all by contact with silicone treated surfaces The authors believe that with perfect technic normal platelet free plasma would be incoagulable in silicone treated tubes

There is no evidence that a silicone surface itself *interferes* with clotting for on the addition of highly dilute thromboplastin to platelet free plasma clotting occurred as promptly in silicone treated as in glass tubes The conclusion is that an inactive thromboplastin precursor in plasma is activated on contact with glass surfaces

These studies seem to show that platelets are probably unnecessary to initiate clotting but that they increase the rate of clotting and the amount of prothrombin consumed in the process There is

Fibrinogen

Horanyi (549) has reported the splitting of fibrinogen into two fractions by a simple method Shinowara (550) noted that the level of the clotting time becomes elevated as the purity of a fibrinogen preparation increases He studied the effect of various plasma protein fractions added to the substrate on the thrombin fibrinogen reaction time (551) In a system of fibrinogen fractions (79 to 80 per cent purity) in citrate phosphate buffer albumin definitely lowered Fractions II III and IV 1 elevated and fractions IV-4 and hemoglobin slightly depressed the clotting times The significance of these findings with fibrinogen fractions prepared by the low salt—low temperature—ethanol principle is discussed

An interesting case report by Moloney Egan and Gorman (552) described a hemorrhagic diathesis in a pregnant woman at term characterized by a critical decrease in fibrinogen Following the administration of blood transfusions and fraction I of Cohn it was possible to remove a dead fetus surgically after which the mother recovered promptly The authors discuss the possible role of fibrinolysin in this type of acquired afibrinogenemia

The Blood Platelets

A technic was devised by Quick Shanberge and Stefanini (553) for varying the number of platelets in samples of plasma without otherwise altering the plasma The following observations were made (a) the greater the number of platelets the sooner clot retraction began and the smaller the final clot (b) the clot retraction was characterized by a relatively long latent period followed by an accelerated phase and protracted completion (c) within a wide range in the number of platelets no significant change in coagulation time was observed (d) as the number of platelets diminished the speed of prothrombin consumption was decreased but within normal limits the final amount of prothrombin converted approximated a fixed value (e) below a critical number of platelets the consumption of prothrombin stopped after a relatively short time suggesting that plasma contains an agent that inactivates the platelet enzyme (f) in thrombocytopenic purpura the consumption of prothrombin may be markedly diminished

their relative proportions in the total platelet count The normal range of adhesive platelets was found to be between 60 000 and 110 000 platelets per cu mm Platelet adhesiveness appeared to be independent of the adhesiveness or sedimentation rate of the erythrocytes The method is relatively simple and can be readily applied to the clinical detection of thromboembolic tendencies

Using the method described Moolten Vroman and Vroman (557) studied platelet adhesiveness in hemorrhagic and thrombotic diseases Platelet adhesiveness was reduced in thrombocytopenic purpura with hypersplenism and in patients under the influence of heparin The hypoprothrombinemia induced by dicumarol had little effect on platelet adhesiveness In hemophilia the platelet adhesiveness was normal or increased

The authors state that hyperadhesiveness with or without an increase in the total platelet count accompanies cellular destruction anywhere in the body during uncomplicated convalescence from operations or accidental trauma in instances of ischemic necrosis such as myocardial infarction or peripheral gangrene in cancer and in such blood dyscrasias as polycythemia vera idiopathic thrombocythemia and essential thrombophilia Advanced degrees of hyperadhesiveness predispose to thrombosis Rapid diminutions in the platelet count particularly of the adhesive platelets are warnings of developing thrombosis In cases of thrombotic disease the blood may be so rapidly depleted of adhesive platelets that purpura occurs

Endocrine Influences on the Platelets

Adams (558) found that adrenal cortical extract failed to influence the platelet count in mice rats or rabbits Adrenalectomy and sham adrenalectomy were followed by almost identical increases in the platelets in mice and rats When adrenal cortical extract or physiological saline were given to adrenalectomized rats there followed a consistent fall in platelets not observed in sham adrenalectomized rats or after giving distilled water to adrenalized rats Platelet levels in hypophysectomized rats were significantly lower than in unoperated controls The maximum rise in platelets following splenectomy in hypophysectomized rats was markedly lower than that following splenectomy in intact rats

a close correlation between the number of platelets present and the amount of prothrombin converted during clotting in glass tubes

Hemophilic platelet free plasmas were invariably spontaneously incoagulable in glass and in silicone tubes at 37° C although they clotted promptly upon the addition of thromboplastin suggesting that the defect in hemophilia is a deficiency of the plasma thromboplastic factor The authors concluded that hemophilia is not caused by any defect in platelets but that the presence of platelets is what makes hemophilic blood clot at all In one hemophilic a hemorrhagic diathesis persisted despite a normal whole blood clotting time This indicates that plasma thromboplastin is necessary for normal hemostasis regardless of the clotting time in vitro Presumably antihemophilic globulin is identical with the plasma thromboplastin precursor

The authors concluded that both the platelet and the plasma factors are apparently necessary for normal coagulation although either one alone is sufficient to initiate coagulation The interaction between platelets and the plasma factor is not yet clear

Hartman Conley and Lalley (555) prepared normal human plasmas of varying platelet concentrations without anticoagulant by centrifuging blood in silicone treated apparatus Essentially platelet free plasma clotted relatively promptly after transfer to glass tubes but coagulation frequently did not occur in silicone treated tubes Increasing the glass surface area in contact with the plasma shortened the clotting time markedly regardless of the platelet concentration Crushed glass was more effective in this respect than was a suspension of macerated platelets

The authors believe that the clot promoting effect of crushed glass on centrifuged plasma is more readily explained by an alteration of the platelet free plasma itself than by the disruption of the few remaining platelets After brief periods of storage plasma often fails to clot on the addition of crushed glass In plasma clotting upon contact with glass the rate of conversion of prothrombin was directly related to the platelet concentration

Moolten and Vroman (556) devised a wick of braided glass wool as an adsorbing filter for the separation of adhesive from non adhesive platelets in citrated blood permitting an enumeration of

CHAPTER 26

Rationale for the Use of the Anticoagulants

CLOTTING IN SILICONE TUBES

THE effect of surface contact on blood coagulation is important in the development of suitable methods for studying the coagulation time of the whole blood the prothrombin time of plasma and in other reacting systems used in research and clinical laboratories Of greater ultimate importance is an understanding of the role of surface contact in the process of intravascular clotting At the present time there is a considerable interest in the reactions of blood and its components in silicone tubes

Margulies and Barker (562) described a method of measuring the coagulation time of whole blood in containers coated with silicone A coagulation time of 30 minutes or more was obtained in 83 per cent of normal subjects and for this reason 30 minutes was regarded as the usual lower limit of normal When blood samples were allowed to stand in silicone coated syringes for as long as 10 minutes following venipuncture no significant difference in the coagulation time was obtained

Among patients with clinical evidence of a tendency to thrombosis a significant number had abnormally rapid silicone coagulation times Patients with thrombophlebitis and with spontaneous intravascular clotting frequently had coagulation times of less than 30 minutes Patients with occlusive arterial diseases usually had normal times

Changes in the prothrombin time in 13 patients receiving dicumarol were associated with corresponding changes in the coagulation time in silicone tubes though not in the coagulation time measured in glass tubes (563) Changes in the silicone coagulation time often lagged behind changes in the prothrombin time The relation between prothrombin time and silicone coagulation time varied from individual to individual so that there was no correlation between the two methods but changes in prothrombin time

No change in the number or morphology of the megakaryocytes occurred following splenectomy either in intact or in hypophysectomized rats

Since an increase in platelet concentration in the peripheral blood usually accompanies infection trauma hemorrhage and asphyxia conditions which stimulate the release of pituitary adrenocorticothrophin (ACTH) the possible effect of the latter was tested by Greer and Brown (559) No change in platelet counts were detected following the administration of hog pituitary tissue or of purified ACTH There was no reduction of circulating lymphocytes in these experiments although a transient polymorphonuclear leukocytosis did occur

Gerheim and Miller (560) studied the effect of exercise on the platelet count Exercise consisted of running a treadmill for five minutes at a speed of seven miles an hour on a grade of 17 5 per cent or on the level for two minutes at 12 miles per hour Blood was obtained before exercise immediately after exercise and 10 30 60 and 90 minutes after exercise There was a 60 to 100 per cent increase in the leukocyte count but no increase in the platelet count The authors suggest that the increased velocity of the circulation may have destroyed the very labile platelets and that this effect may have masked any platelet increase

There have been 15 or more cases reported of a rapidly fatal anemia in which mutiple visceral hyaline thrombi composed of platelets have been demonstrated within arterioles and capillaries at autopsy *Thrombi were frequently surrounded* by proliferating cells from the vessel walls In presenting another such case Muirhead Crass and Hill (561) described a diffuse proliferative glomerulitis which has not previously been emphasized in association with platelet thrombosis

acute thrombophlebitis They described experiments in rabbits which showed that heparin alone is not effective in preventing the formation or causing the solution of an intravascular clot in the presence of acute thrombophlebitis The combined administration of heparin and penicillin however prevented or caused the disappearance of a clot in a large number of animals with experimentally produced acute thrombophlebitis

Heparin and Platelets

Fidler and Jaques (566) confirmed the fact that heparin added to dog s blood fails to preserve the platelets although citrate does preserve them The intravenous injection of heparin lowers the platelet count in dogs

The intravenous injection of heparin also produced a moderate and transient fall in the platelet count in man Heparin added to human blood in vitro also lowered the platelet count Different samples of commercial heparin of the same anticoagulant strength show different effects on platelets With some samples the effect is very small

To evaluate the significance of the reported increased susceptibility of thrombocytopenic blood to heparin Conley Hartmann and Lalley (567) studied the clotting times of platelet free and platelet rich plasmas prepared in silicone coated apparatus which were mixed in different proportions and contained graded concentrations of added heparin They concluded that the magnitude of the clot inhibitory effect of heparin is inversely proportional to the number of platelets present and that the increased susceptibility of thrombocytopenic purpura blood to the action of heparin is attributable to the reduced platelet concentration rather than to a supplemental anticoagulant effect introduced by the presence of hypothetic heparin like substance The results further suggest that the concentration of active heparin normally present in plasma is minute i e 0 0005 mg /ml or less

Dicumarol and Experimental Thrombosis

Of great clinical interest is the relation between the degree to which prothrombin activity is reduced and the effectiveness of dicumarol therapy in preventing intravascular clotting Two re

were accompanied by changes in silicone coagulation time predictable in direction if not in magnitude

Conley Hartmann & Lalley (564) used silicone treated apparatus to obtain blood from normal human subjects without the use of anticoagulants The formed elements were removed by high speed centrifugation at low temperatures Direct microscopic examination of the undiluted plasma revealed as a rule less than 10 platelets per cubic millimeter In some instances no platelets were seen Plasmas prepared by this manner regularly clotted within a few minutes at 37° C following the addition of ground glass

Platelet extracts prepared by grinding washed platelets in glass containers also brought about coagulation However the concentrated platelet extracts did not cause coagulation to occur more rapidly than did ground glass when added to these essentially platelet free plasmas The rate of clot formation following the addition of ground glass was related to the amount of glass added and was independent of the number of platelets or quantity of platelet extract present The amount of prothrombin converted during coagulation seemed directly related to the amount of platelet material available When plasma was clotted by ground glass in the virtual absence of platelets prothrombin consumption seemed negligible Unlike normal plasma hemophilic plasma deprived of its platelets failed to clot on contact with glass

Normal platelet deficient plasma could be kept in silicone treated tubes at 37° C for relatively long periods of time without spontaneous coagulation even though clotting occurred promptly following the addition of ground glass Although fresh normal plasma invariably clotted on contact with glass portions of this plasma stored for 24 hours at 2° C in some instances failed to clot on the addition of ground glass

These observations suggest that the initiation of coagulation by surface contact may be brought about by alterations produced in the plasma itself and not necessarily by platelet changes

Heparin and Experimental Thrombosis

Rabinovitch and Pines (565) undertook to determine whether heparin alone or in combination with penicillin could bring about the solution of a clot in the presence of experimentally produced

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cent studies of experimental thrombosis in dogs have attempted to clarify this question In both instances a reduction of prothrombin activity to approximately 35 to 40 per cent appears necessary for therapeutic success Taking into account such factors as differences between species differences between experimental and clinical conditions and the necessary factor of safety in man we would interpret these results as compatible with a reduction *in prothrombin activity to the neighborhood of 30 per cent in the* clinical application of dicumarol

Moss Schafer and Kirby (568) have studied the anticoagulant effect of dicumarol at various prothrombin levels in dogs In control animals thrombosis occurred in cannulated femoral arteries in from three to 10 minutes (average 6 3 minutes) In animals treated with dicumarol there was no significant delay before the appearance of thrombi until the prothrombin levels were reduced to 40 per cent or less of normal At this prothrombin level the time of appearance of thrombi averaged 16 6 minutes The line of demarcation was sharp at 40 per cent but at 10 20 and 30 per cent of normal further retardation in the occurrence of thrombosis was not significant

Holden Cameron Shea and Shaw (569) anesthetized dogs lightly with sodium pentobarbital and isolated segments of veins with soft rubber clamps A minimum amount of either trypsin or thrombin solution was injected and after 15 minutes the vein was opened and inspected Similar experiments were done on dogs who had been given dicumarol It was found that experimental thrombi could be prevented by reducing the prothrombin activity to 35 per cent of normal as determined by Brambel s method

Owen and Bollman (570) present evidence obtained from experiments on dicumarolized dogs which suggests that the hemorrhagic diathesis produced by dicumarol is attributable not alone to a disappearance of prothrombin but also to the loss of a factor the function of which is to facilitate the conversion of prothrombin to thrombin Variations in the concentration of this conversion factor present in plasma serum or serum pseudoglobulin may explain the familiar discrepancies in the results of one and two stage methods of estimating prothrombin activity It may also account for the therapeutic efficacy of serum in the

treatment of cattle with sweet clover disease a phenomenon otherwise difficult to explain

Comparative Studies of Heparin and Dicumarol

Loewe Hirsch Grayzel and Kashdan (571) induced clotting in the jugular veins of adult rabbits Nine to 14 days after the production of thrombosis heparin or dicumarol was administered to alternate animals respectively for a period of two weeks Sufficient anticoagulant was given to maintain either the coagulation time or the prothrombin time well above clinically accepted limits

The authors found that in the presence of heparin all clots underwent resolution if they were in the sludge stage Dicumarol did not produce this response because of the time lag between the administration of the drug and the effective prolongation of the prothrombin time However beyond this initial stage both anticoagulants effectively caused resumption to clinical patency in a considerable number of veins which were occluded by clots for from four days to two weeks This effect is at variance with the commonly accepted knowledge of thrombus behavior The degree of recanalization appeared to be greater with heparin On the basis of this comparative study the authors concluded that heparin is superior to dicumarol as an anticoagulant

Martin Laufman & Tuell (572) employed direct micrometry of small caliber vessels in dogs to determine the effects of various therapeutic measures on the behavior of these vessels following main stem occlusions Sludge formation occurred within a relatively short time after either arterial or venous occlusion and appeared to be a precursor to thrombosis Heparin and dicumarol prevented thrombus formation in such cases but did not alter the character of the sludge apppreciably The fact that vasodilating agents are not capable of producing a favorable effect in thrombosed small vessels implies that the use of anticoagulants should be an integral part of therapy in acute main stem occlusions

Kiesewetter and Shumacker (573) undertook to compare under controlled experimental conditions the reliability of heparin and dicumarol in the prevention of arterial and venous thrombosis The common carotid arteries the external jugular veins and the femoral arteries and veins of healthy mongrel dogs were used

The arteries were dissected free and blood was excluded from a one to two inch segment by a rubber band tourniquet The artery was transected through half its circumference and was then closed roughly by a continuous silk suture The carotid arteries were cut and closed transversely the femoral arteries were cut transversely but closely longitudinally to produce a definite narrowing Veins were dissected free and blood expelled from a one to two inch segment The isolated segment was then distended maximally with 5 per cent sodium morrhuate solution for three to four minutes The morrhuate was then withdrawn by aspiration and blood flow permitted to resume

The administration of anticoagulants was begun prior to operation so that an effective level was present when the vessels were traumatized Dicumarol was administered intravenously in a solution containing 10 mg per cc The drug was given 24 hours preoperatively in a dose of two to three mg per kg body weight It was given thereafter according to the prothrombin time in doses of one to two mg per kg body weight Crystalline heparin was given intravenously immediately before operation and thereafter at intervals of two to four hours Dosage ranged from 0 5 to 4 mg kg body weight Heparin/Pitkin menstruum was given subcutaneously or intramuscularly in dose of 5 to 10 mg per kg body weight

Before and each day following operation blood was withdrawn by venipuncture for determination of the coagulation time (Lee White method) fibrinogen level (technic of Mylon Winternitz and de Suto Nagy) and prothrombin time (Quick method for whole plasma Wright Prandoni modification for 25 per cent diluted plasma)

Experiments were carried out on 84 dogs but only 70 of these were satisfactory for statistical comparison Fifteen dogs served as controls 25 received dicumarol in varying amounts and 30 were heparinized Altogether 228 veins and 177 arteries were traumatized and subsequently examined for thrombosis Except in certain instances vessels were not reexamined postoperatively until seven days after the operative trauma

Among the 15 control animals thrombosis occurred in 91 per cent of the veins 83 3 per cent of the small arteries and 70 per cent of the large arteries Blood studies on the control animals showed

that the coagulation time was generally shortened on the first post operative day There was a measurable hyperprothrombinemia in five of nine dogs but this persisted in only four Despite great variation from day to day the fibrinogen determinations showed a rise on the first or second day and then fell gradually to normal

Among 11 dogs given crystalline heparin before operation and every four hours thereafter (some were given heparin/Pitkin menstruum every evening to tide them over to morning) the incidence of thrombosis at the end of the period of treatment was 56 3 per cent in the veins 6 7 per cent in the small arteries and 9 5 per cent in the large arteries There were wide variations in the clotting times performed from time to time and a prolonged clotting time was generally not maintained in any animal for the duration of the experiment There was a significant hyperprothrombinemia *in one animal and a hypoprothrombinemia in only two in* stances where the coagulation time was markedly prolonged The fibrinogen studies were similar to those in the controls

Fourteen dogs were given large doses of heparin in Pitkin menstruum sufficient to produce a constant and effective prolongation of the clotting time for 24 hours 48 hours or 72 hours Venous thromboses occurred as follows

	Heparinized with heparin/Pitkin menstruum for			
	24 hours	48 hours	72 hours	Total
Per cent venous thromboses				
At end of treatment	9 1	20 8	0	12 9
At end of 7 days	45 5	66 7	57 1	56 7

Five dogs were given only a single dose of heparin (2 mg kg body weight) intravenously just prior to operation After one week 62 5 per cent of the veins 10 per cent of the small arteries and 30 per cent of the large arteries were thrombosed

In 10 animals treated with dicumarol before and for an average of six days after operation and in which the per cent of pro thrombin activity was kept consistently low thrombosis occurred in 41 4 per cent of traumatized veins 50 per cent of the small arteries and 13 8 per cent of the large arteries The prothrombin

levels were almost uniformly low the blood fibrinogen levels did not differ materially from the controls and the coagulation times were generally prolonged when the prothrombin activity was below 20 per cent of normal

In four dogs whose prothrombin levels were not constantly maintained the incidence of thrombosis was 75 per cent for veins 75 per cent for small arteries and 42 9 per cent for large arteries The veins of six dogs were traumatized and excessive amounts of dicumarol were given for the first 24 or 48 hours The anticoagulant effect was then terminated by blood transfusion and the parenteral administration of vitamin K The incidence of venous thrombosis was 16 7 per cent at the end of treatment and 47 6 per cent of the end of a week Five dogs were given a single dose of dicumarol (5 mg per kg body weight) 24 hours before operation One week postoperatively thrombosis had occurred in 75 per cent of traumatized veins none in the small arteries and in 44 4 per cent of large arteries

When the incidence of thrombosis from five to seven days post operatively in the untreated animals *in the animals heparinized for this length of time* and *in the adequately dicumarolized animals* (prothrombin level fairly constant at 30 per cent or less) are compared the figures are as follows

Anticoagulant treatment	Incidence of thrombosis in per cent		
	veins	small arteries	large arteries
none	85 2	92 0	66 7
heparin	61 5	9 1	11 8
dicumarol	46 2	50 0	17 6

There is no statistical difference in the incidence of thrombosis in veins and large arteries between the groups treated with heparin or with dicumarol The incidence in the small arteries is significantly higher in those treated with dicumarol than with heparin

In animals untreated and in those treated intensively with heparin or dicumarol for periods of 24 to 48 hours the incidence of venous thrombosis was 100 per cent in the control group but

only 15 2 per cent in those treated with heparin and 16 7 per cent in those treated with dicumarol The administration of single doses of heparin or of dicumarol had little demonstrable efficacy in lowering the incidence of venous thrombosis

Of 35 animals treated with heparin 25 (71 4 per cent) had evidence of subcutaneous hemorrhage Nineteen (76 per cent) of these were massive three (12 per cent) were so severe as to require ligation and nine animals (36 per cent) died of postoperative hemorrhage Of 25 dogs treated with dicumarol 11 (44 per cent) bled subcutaneously Five (45 5 per cent) of these were large none required arterial ligation and three animals (27 3 per cent) died as a result of hemorrhage Among the 28 dogs given heparin in Pitkin menstruum 16 (57 1 per cent) had some serious complication five (17 9 per cent) developed a slough nine (32 1 per cent) had marked edema and inflammation and two (7 1 per cent) died of gas gangrene

Kiesewetter and Shumacker warn that certain cautions are necessary in interpreting these results In the long term experiments heparin was given in amounts and at intervals generally inadequate to maintain a constant prolongation of the coagulation time In similar experiments dicumarol was given to maintain prothrombin levels which the authors consider hazardous clinically The experimental conditions of arterial and venous damage were of an extreme degree Significant hemorrhage was rare in venous trauma and occurred usually from along the suture line in arterial trauma

The authors concluded that under the conditions of these experiments dicumarol and heparin appeared equally effective in reducing the incidence of venous thrombosis that anticoagulant therapy was more effective in preventing arterial than venous thrombosis and that statistically superior results were obtained with heparin than with dicumarol in preventing thrombosis of injured small arteries though not large arteries

The Effect of Heparin and Dicumarol on the Coronary Arteries

Gilbert and Nalefski (574) did not believe that the lower mortality and fewer embolic accidents reported in patients treated

with heparin and dicumarol could be due to the anticoagulant action alone They performed experiments on dogs which showed that heparin and dicumarol increase the coronary blood flow The effect of heparin was moderate but with dicumarol it was definite and comparable to that of the xanthines though of longer duration It was evident from this effect of dicumarol on the empty beating heart that the action must be directly on the vessel walls The authors cite the experience of other observers who noted that toxic doses of dicumarol produce a marked peripheral vascular dilatation in the smaller vessels This suggests that hemorrhage following the administration of dicumarol may be due to a gross vascular effect in addition to the effect on the prothrombin concentration

CHAPTER 27

The Use of the Anticoagulants Clinically

Indications

HINES and Barker (575) assert that anticoagulant therapy is the best method for preventing thrombosis and embolism which is available at present They list the following situations in which the use of anticoagulants may be advisable in chronic cardiovascular disease and those cardiovascular diseases in which these situations may arise

Situations in which the use of anticoagulants may be indicated

- I Long term treatment of the disease (only in special situations)
- II Prevention of recurring episodes of thrombosis
- III Treatment of single episodes of thrombosis or embolism
  - A Acute arterial occlusion (including coronary artery occlusion)
  - B Acute thrombophlebitis or phlebothrombosis
  - C Pulmonary embolism or infarction

Chronic cardiovascular conditions or diseases in which anticoagulant therapy may be indicated

- I Occlusive arterial diseases
  - A Thromboangiitis obliterans
  - B Arteriosclerosis obliterans
  - C Simple thrombosis
    - 1 Idiopathic
    - 2 Secondary to
      - a Polycythemia ver
      - b Malignancy
      - c Infection
- II Venous diseases
  - A Primary varicose veins
  - B Chronic venous insufficiency
  - C Recurring idiopathic thrombophlebitis

III Cerebral thrombosis
IV Cardiac diseases
A Cardiac infarction
B Cardiac fibrillation
C Congestive heart failure

In the chronic occlusive arterial diseases thromboangiitis obliterans and arteriosclerosis obliterans the final complete occlusion is usually due to thrombosis Long term anticoagulant therapy as a prophylactic is not practical in all instances of occlusive arterial disease but is indicated in patients with thromboangiitis obliterans who have frequently recurring attacks of thrombophlebitis and in instances of sudden arterial occlusion especially if frequently recurrent

The authors report that they have given dicumarol to 76 patients with Buerger s disease or arteriosclerosis obliterans for as long as four to six months Dicumarol was given to 40 patients with active occlusive disease and to 36 patients prophylactically after amputation In none of these cases was there any evidence of recurrence or extension of arterial or venous thrombosis during the period in which dicumarol was given

The best type of anticoagulant therapy in sudden arterial occlusion is a combination of heparin and dicumarol Without anticoagulants further thrombosis occurs in collateral vessels relieved of arterial spasm or by propagation of an initial thrombus proximally Emboli may arise from the source of an initial embolism or from an initial peripheral thrombus The authors report that they have treated 11 patients with arterial embolism and 16 patients with acute arterial thrombosis of the extremities promptly with anticoagulants The involved extremities were saved in 10 instances of embolism and in 13 of thrombosis

They advise anticoagulant therapy with dicumarol for seven to 10 days in cases of thrombosis of the greater saphenous system of the deep veins of the calf or in instances elsewhere when localized thrombophlebitis extends They also recommend dicumarol for patients with chronic venous insufficiency who are bed ridden for periods of several weeks Anticoagulants are valuable in cases of recurrent idiopathic thrombophlebitis to prevent extension of the venous thrombosis or occurrence of thrombosis

elsewhere in the venous system Long term anticoagulant therapy is indicated only when the recurrent attacks of venous thrombosis occur frequently

Anticoagulants are useful in preventing extension of a cerebral thrombosis but great care must be exercised to avoid excessive depression of the prothrombin level and consequential hemorrhage It is necessary to distinguish carefully between cerebral thrombosis and cerebral hemorrhage and examination of the cerebrospinal fluid is indicated before administering anticoagulants

The authors cite the experience at the Mayo Clinic with dicumarol in coronary occlusion with myocardial infarction Although the mortality rate has not been greatly reduced there has been a striking decrease in the incidence of thromboembolic complications when anticoagulants have been used In no instance has there been serious hemorrhage which was considered due to the anticoagulants

Hines and Barker suggest also the use of dicumarol in patients with rheumatic heart disease and auricular fibrillation who experience repeated peripheral emboli and in selected instances of congestive heart failure They outline methods of administration of heparin and dicumarol which are essentially those described in this monograph

There is a comprehensive discussion of many aspects of anticoagulant therapy in cardiovascular disease by Nichol Falk Meneely and Hull (576) who presented a panel discussion of the subject before the Southern Medical Association in October 1948

Venous Thrombosis and Pulmonary Embolism

Smith and Mulligan (577) reported the prophylactic use of dicumarol against the development of postoperative thromboembolism in 2 353 women undergoing major and vaginal plastic surgery Several dosage schedules were used as follows (1) 200 400 mg during the 40 hours preceding operation (2) 100 200 mg after 10 days if the patient was still in bed and (3) 50 mg within 48 hours following operation and again after five to 10 days

The results of this study are most conveniently compared by indicating the incidences of thromboembolism in three groups of patients

	Incidence of Thromboembolism	Incidence of Non fatal Emboli	Incidence of Fatal Emboli
Prior to 1943 when dicumarol prophylaxis was initiated	1 90	1 432	1 484
Following 1943 9 051 patients of whom 2 353 received dicumarol	1 215	1 1131	1 3017
Following 1943 2 353 patients receiving dicumarol	1 138	1 1177	1 2353

Hemorrhagic complications including hematemesis hematuria vaginal hemorrhage and subarachnoid bleeding were the only complications of dicumarol therapy occurring 26 times or in one out of every 91 patients treated One fatal subarachnoid hemorrhage occurred and the patient was found at autopsy to have multiple small aneurysms of the Circle of Willis along with organized and recent hemorrhage

The authors concluded that on the basis of these observations the use of dicumarol in 2 353 selected patients out of a total of 9 051 operated upon during a four year period appears to have contributed to a considerable reduction in the incidence of postoperative thrombotic complications without in itself causing a distressing amount of trouble

J P Strombeck (578) evaluated early ambulation and anticoagulants in the prevention and treatment of thrombosis and embolism and outlined a plan of treatment for these conditions A fundamental factor in the development of venous thrombosis is in his opinion the retardation of venous return from the thrombosed area

Among 940 patients given dicumarol prophylactically 29 (3 1 ± 0 57 per cent) developed thrombosis Early ambulation was prescribed for 891 patients and 50 of these (5 6 ± 0 76 per cent) developed thrombosis When the figures were adjusted to account for those for whom dicumarol was contraindicated or in whom operations of a type rarely followed by thrombosis were performed

the favorable results of dicumarol prophylaxis became statistically significant This group showed clearly a lowered incidence of thrombosis

The frequency of thrombosis was the same among men who received dicumarol as it was among those on early ambulation alone Women given dicumarol had a lower incidence of thrombosis than those on early ambulation Fatal pulmonary embolism did not occur among those receiving the drug but did occur in four patients on early ambulation

Strombeck recommends early ambulation as the fundamental and most important measure in prevention of thrombosis It should be started the first day or at the latest two or three days after operation It should be supplemented especially in women by dicumarol prophylaxis the day after operation and continued until the patient is fully mobilized He advises that the prothrombin activity be maintained between 10 and 30 per cent of normal

Strombeck urges that physicians and nurses be trained to recognize early signs and symptoms of thrombosis so that combined heparin and dicumarol therapy may be started as soon as possible According to Allen early thrombosis must be stopped within 24 hours if the risk of embolism is to be avoided

The results of treatment of 92 cases representing 105 extremities with deep thrombophlebitis were reported by Felder (579) together with a detailed discussion of the diagnostic signs methods of treatment type of venous thrombosis and the primary disease process For practical purposes both the bland and inflammatory thromboses were called thrombophlebitis With the exception of eight patients who were treated with vein ligation anticoagulants (dicumarol and heparin) were used with an average of 10 days of bed rest usually in mild Trendelenburg position

Although most of the patients had had one pulmonary embolism at the time of the diagnosis of thrombophlebitis anticoagulant therapy reduced the incidence of secondary embolism from an expected 30 per cent to 2 17 per cent and that of secondary fatal embolism from an expected 25 per cent to zero An analysis of the primary condition indicated the importance of prophylactic postoperative anticoagulant therapy in patients with cancer and in

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TABLE XIII—(*Continued*)

Authors Refere ces		Pts	Drug	M t	T E Compl	H m C mpl
Greisman d Ma cus *Am He t J 36* 600 Oct ber 1948	T	75	Dicum rol	7 (9%)	3 (4%)	3 n ne m j
	C	100		35 (35%)	21 (21%)	
C m h el & Oett ng *Naval M Bull 49* 12 Jan Feb 1949	T	30	D cumarol	4 (13 3%)	2 (6 ,%)	5 (16 6%)
	C			7 (16 3%)	12 (27 9%)	2 (4 6%)
Fu man et l *Abst Am F d Cl n Rese h* 1949	T	,4	Not stated	(19%)	(5%)	2 mild
	C	240		(40%)	(11%)	
F est & Taylo *Ab t Am Hea t M t J e* 1949	T	71 (73)	D cum rol	(4) (20%)	(10 6%)	2 m or
	C	54		(22 5%)	(25 0%)	
Schill g F J *Abst Am H t Me t* Jun 1949	T	60	D cumarol Comb n d	(16%)	3 2 f t l	
	C	60		(40%)	23 8 f tal	
Loewe & F1b *Am H t J 37* 701 April 15 1949	T	20	H pa in/ P tk ns	1 (5%)	14 pre Rx 0 on R	
	C	one				
W ght M rple & Beck *Am H t J 36* 801 Dec 48 *J A M A 138* 1074 Dec 11 1948	T	432	D marol Combi ed	15%	(5) (11%)	1 100 c ses
	C	368		24%	(6) (25%)	6/100

Comb ed ther py Hepa adm tered d ing fi t f w d ys of d m rol ther py
T Tre ted cases
C C trol c
(1) 43 m lt ple coro y or pe f he l episod 11 (25%) death
33 uncompl c t d 1st 2 d tt ks 4 (12%) de ths
(2) Ser es of N y and B r es *Am H t J 30* 65 J ly 1945
(3) Myocard al rupt w th d ths
(4) Am ng surv ors for m th 24 h rs
(5) T t d c 14 c mpl c t o per 100 p t ts
(6) Control c ses 36 compl c t o s pe 100 p t e ts

TABLE XIII

SUMMARY OF THE RESULTS OF ANTICOAGULANT THERAPY IN THE TREATMENT OF CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION AS REPORTED IN THE LITERATURE

Authors References		Pts	Drug	Mort	T E Compl	Hem Compl
Wright I S Proc Am Fed Clin Research 2 101 Dec 1945	T	76 (1)	Dicumarol	15 (19 7%)		Clin 0 Post 0 8
	C	none				
Holten C *Saert yk fr Nordisk Med 31* 2146 1946	T	80	Heparin & Combined	22 (25%)	4 in 26 posts	
	C	77		38 (49%)	15 in 41 posts	
Nichol & Fassett *South M J 40* 631 August 1947	T	64 (70)	Dicumarol	11 (15 %)	0 in 6 posts	
	C	none				
Peters D ence & Br m bel *South M J 41* 526 June 1948	T	110	Dicumarol	12 (10 9%)	1 (0 9%)	1 minor
	C	86		22 (25 5%)	13 (15 1%)	
Parker & Barker *Proc Staff Meet Mayo Clin 23* 367 Aug 4 1948	T	99 (100)	Dicumarol Combined	11 (11%)	5 (5%)	8 none severe
	C	100 (2)		13 (13%)	37 (37%)	
Glueck et al *Am Heart J 35* 269 February 1948	T	44	Combined	9 (20%)	3 (7%)	3 (3) 1 death
	C	44		19 (45%)	12 (27%)	
Vand V er et al *Trans Phila C l Phy 16* 67 June 1948	T	35	Dicumarol	3 (8 6%)	6 (17 1%)	2 gro
	C	51		18 (35 3%)	12 (23 5%)	
McC ll M *Am J Med Sc 215* 612 June 1948	T	71	Dicumarol	9 (12%)	2 both fatal	5 3 gross
	C	no				
Reich & Eisenmenger *Am J Med Sc 215* 617 June 1948	T	24	Dicumarol	4 (16 7%)		
	C	non				

arise from organization of mural thrombi and has traced this process from the earliest deposition of fibrin to the formation of massive deposits with atheromatous softening Duguid concluded that atherosclerosis depends not only upon changes in the tissues with the walls of the vessels but upon changes in factors governing fibrin formation in the circulation

Harrison (587) produced lesions indistinguishable morphologically from those of arteriosclerosis in the pulmonary arteries of rabbits by injecting finely fragmented fibrin clots into the ear veins

Gibson concluded that a clotting tendency is an essential feature of coronary thrombosis and is also the basis of the local lesion which determines the site of such thrombosis On this basis he advocates the use of anticoagulant therapy as an essential part of the treatment of coronary thrombosis

Carmichael and Oetting (588) observed 73 patients with acute coronary thrombosis and myocardial infarction of whom 43 were treated by the usual conservative measures only and 30 were treated similarly except that they were given dicumarol A few patients received heparin initially The selection of patients excluded from the study those (1) dying within 36 hours of admission (2) in whom the occlusion had occurred more than four days previously and who had been treated adequately during that interval (3) for whom the diagnosis was not established by the fourth hospital day and (4) who exhibited a contraindication to dicumarol therapy

A preliminary prothrombin time was done The initial dose of dicumarol was 300 mg and the dosage thereafter was determined by the prothrombin time An effort was made to keep the prothrombin concentration between 15 and 30 per cent of normal Prothrombin times were determined by Quick s method

When heparin was used 300 mg was given in the liter of 5 per cent dextrose intravenously at the rate of 20 drops a minute The coagulation time was determined by the capillary tube method every four hours An attempt was made to keep the coagulation time between 18 to 24 minutes

Twelve patients or 27 9 per cent of those in the control group suffered thromboembolic complications clinically There were

those undergoing major gastrointestinal surgery hysterectomies and hip fixations

Both anticoagulant therapy and vein ligation have a place in the prevention and treatment of thromboembolism The indications for each should be determined on the basis of the type of thrombophlebitis the underlying disease and condition of the patient the availability of laboratory control and the estimated risk of fatal embolism It is quite possible that the incidence of death from pulmonary embolism in untreated patients is lower than generally believed

Ball and Hughes (580) reported an analysis of 100 patients treated with anticoagulants and discussed the hazard of venous thrombosis with the treacherous complication of sudden pulmonary embolism Venous thrombosis was found to be a common condition particularly in medical patients Heparin combined with dicumarol proved to be an effective method of treatment Since the administration of dicumarol requires careful laboratory control the authors adopted the use of the one stage method of Quick They conclude that with the early diagnosis of thrombosis in the leg veins both pulmonary embolism and chronic leg ulcers can be prevented

Acute Coronary Occlusion with Myocardial Infarction

Bean (581) has listed the considerations which form the basis for the use of anticoagulants in the treatment of patients with acute myocardial infarction

Gibson (582) has emphasized the role of intravascular clotting in the genesis of coronary thrombosis He cites Bourne (583) who pointed out that the majority of persons with atheromatous coronary arteries die without coronary thrombosis whereas some persons die of coronary thrombosis who have little coronary atherosclerosis Bourne reported five cases in which coronary thrombosis coincided with thrombosis elsewhere in the body Meakins and Eakins (584) found that all but four of 62 patients with coronary thrombosis had thromboses in the arterial or venous systems at autopsy

Duguid (585 586) has claimed that atherosclerotic lesions may

group of patients receiving dicumarol (6) serious hemorrhage complicating dicumarol therapy is uncommon (7) larger doses of dicumarol administered during the initial 48 hours may produce a higher percentage of satisfactory prothrombin levels during the early stages of treatment (8) adequate anticoagulant therapy will reduce the hazard of embolization by portions of mural thrombi when quinidine is given to regulate cardiac arrhythmias and (9) *in view of the apparent efficacy of dicumarol in the treatment of myocardial infarction it would seem justified to include anticoagulant therapy as part of the active therapeutic regimen for all patients having this condition and otherwise suited to this therapy*

Seventy four patients with coronary thrombosis and treated with anticoagulants at the Vanderbilt University Hospital during 1947 48 were sorted into categories of known prognostic import and studied by Furman Gale Billings and Meneely (589) This group was then compared with a control group of 240 patients with coronary occlusion but not treated with anticoagulants selected from the files of the Vanderbilt Hospital for the years 1925 1946

The incidence of extracardiac thromboembolism in the control group was 11 per cent in the treated group it was five per cent The mortality rate in the control group was 40 per cent in the treated group it was only 19 per cent

The mortality among those treated patients exhibiting grave prognostic signs and symptoms (especially those of congestive failure or shock like states) was higher than that for the treated group collectively However the beneficial effect of anticoagulants carried over in varying degree to most of these groups

The authors conclude that the beneficial effect of anticoagulants in the treatment of arteriosclerotic coronary thrombosis must result from some action other than or in addition to the prevention of extracardiac thromboembolic phenomena The nature of such an action is not apparent from this study

Freston and Taylor (590) divided 127 patients with acute myocardial infarction into two groups one consisting of 71 patients with 73 admissions was treated with dicumarol when the diagnosis could be established without delay the other consisting of 51 patients admitted to another service during the same period of one year served as control

eight secondary myocardial infarctions four pulmonary infarctions three instances of thrombophlebitis and one mesenteric thrombosis Two patients or 6 7 per cent of those treated with dicumarol suffered vascular complications One of these was a secondary myocardial infarction and the other was a renal infarct

Seven patients or 16 3 per cent of those in the control group died Four patients or 13 3 per cent of those treated with dicumarol died Two or 28 5 per cent of the control patients who died had thromboembolic complications which were reported as the cause of death Of the 4 patients in the treated group who died none had vascular complications Six of seven deaths in the control group and all deaths in the treated group were due to heart failure

Two control patients suffered a hemorrhage in both instances mild rectal bleeding while under observation Among the treated cases hemorrhages occurred in five patients (16 6 per cent) These included two instances of mild epistaxis two instances of mild gingival bleeding and one gastrointestinal hemorrhage treated successfully by the administration of vitamin K parenterally and transfusions

An attempt was made to keep the prothrombin activity reduced to about 30 per cent of normal This level was attained within 12 hours after the first dose of dicumarol in 14 3 per cent of patients within 36 hours in 53 6 per cent of patients within 60 hours in 64 3 per cent of patients and within 84 hours in 96 4 per cent of patients In all cases but one the desired level was reached within 3 5 days

Among the conclusions reached by the authors the following warrant emphasis (1) dicumarol apparently does not adversely affect the cardiac functions during or immediately after the healing stage of infarction (2) digitalis appears to be administered more safely to patients who are under adequate anticoagulant control (3) the administration of dicumarol has no effect on the degree or duration of the pain of acute coronary thrombosis (4) dicumarol therapy significantly reduces to less than one fourth the number of thromboembolic complications (5) the slight difference in mortality in this series might have been increased if the incidence of cardiac enlargement of multiple attacks of coronary thrombosis and of shock had not been slightly greater in the

In the reports cited thus far anticoagulant therapy has consisted largely or exclusively of the administration of dicumarol Except in an occasional instance heparin was administered concurrently with dicumarol and was given only during that period of 48 to 72 hours at the beginning of anticoagulant therapy during which dicumarol is known to be not fully effective In most studies heparin has been an adjuvant designed to protect the patient during the initial period of dicumarol therapy No attempt has been made to assess the value of heparin alone as an anticoagulant in the treatment of coronary occlusion with myocardial infarction

It is therefore of considerable interest that Loewe and Eiber (592) have reported recently the results of treatment with heparin/Pitkin menstruum in twenty consecutive unselected patients with acute coronary artery thrombosis and myocardial infarction All patients were acutely ill and the majority had serious complications Ten patients were seen from three to 72 hours after onset The remaining 10 patients were seen from six to 56 days after the acute occlusion

An initial dose of 400 mg heparin/Pitkin menstruum subcutaneously was followed usually by 400 mg every other day for three to four implants The frequency and dosage of individual injections (200 to 400 mg) was then regulated by the response of the coagulation time of the whole blood as determined by the method of Lee and White effective heparinization requiring that the coagulation time be prolonged to at least three times normal (30-45 minutes)

Loewe and Eiber state that the three purposes of anticoagulant therapy in coronary occlusion with myocardial infarction are (1) to prevent the propagation of the coronary thrombus (2) to prevent embolization from mural thrombi and (3) to prevent thrombosis of the deep venous channels They discuss the comparative advantages and disadvantages of heparin/Pitkin menstruum and dicumarol

The authors summarize their experience as follows Anticoagulation therapy with heparin/Pitkin menstruum was the subject of an exploratory study in 20 consecutive unselected patients with acute coronary artery thrombosis and myocardial infarction

All of the patients in the series were seriously ill some were

Omitting the patients who died during the first 24 hours in the hospital, the mortality rate of the survivors was 22.5 per cent for the control group and 25.8 per cent for the treated group. If the 13 patients in the treated group who did not receive dicumarol because of the failure to diagnose infarction promptly are omitted, of 45 patients who actually received the drug the mortality rate was 20 per cent.

There was a marked reduction in thromboembolic complications in the treated group. The incidence among the controls was 25 per cent, that among the treated patients 10.6 per cent. Six complications occurred in patients less than 60 years of age, 12 in patients 60 years or older. The majority of these patients were in congestive heart failure or had been when the coronary attack occurred. Only two incidences of minor genito-urinary bleeding occurred in the patients treated with dicumarol.

The authors conclude that (1) dicumarol is reasonably safe to use in the presence of myocardial infarction although it is not an ideal anticoagulant, (2) there is a significant drop in the incidence of thromboembolic complications when dicumarol is administered, (3) the frequency of thromboembolism increases in persons over 60 years of age, suggesting that anticoagulants be used in this group particularly in the presence of congestive heart failure, (4) the difference in the mortality rate is not convincing.

The report by Schilling (591) is based upon the observation of 120 patients with myocardial infarction, 60 of whom received dicumarol and heparin or dicumarol alone. The Link-Shapiro method was used for the determination of the prothrombin time. The author found that the use of 12.5 per cent diluted plasma was of greater value in following the course of the dicumarol therapy than was the use of whole plasma. He advocates the use of heparin in all cases of myocardial infarction because of a state of hypercoagulability existing during the early phases of myocardial infarction.

The mortality in the control group was roughly 40 per cent, that in the treated group 16 per cent. Thromboembolic complications contributed to the death of eight patients among the controls and of two patients among the treated cases. There were 23 thromboembolic complications in the control group and only three in the treated group.

there was cerebral hemorrhage due to rupture of a right ventricular striate artery Of the four patients not autopsied two died of recurrent coronary thrombosis

Of the 49 patients remaining on dicumarol all have been active in business or household duties but four have experienced episodes of acute coronary insufficiency without infarction followed by recovery without complication The patient who had been on dicumarol for five years had three attacks of coronary thrombosis before dicumarol therapy but none since Many patients comment upon the abatement of anginal pain while taking dicumarol The authors do not claim that coronary thrombosis can be prevented by this therapy but feel that they have demonstrated that the regime is feasible providing accurate prothrombin determinations can be obtained

Foley (594) has recently summarized and brought up to date the experience which he and Irving Wright had with long term anticoagulant therapy in patients with rheumatic heart disease coronary occlusion and phlebitis migrans Nineteen patients have been maintained on dicumarol without mishap for a minimum of 15 months and some patients have been carried for as long as three years

Congestive Heart Failure

Patients with congestive heart failure are prone to develop thromboembolic complications which increase the morbidity and the mortality of congestive heart failure Kinsey and White (71) reported the presence of pulmonary infarction in no less than 24 of 50 autopsied cases of congestive heart failure Carlotti and his associates (72) in a study of pulmonary embolism in 273 medical cases found that the admission diagnosis in 104 instances had been congestive heart failure

On the other hand patients with liver damage are apt to have a reduced plasma prothrombin activity and to react in an extremely sensitive manner to a given dose of dicumarol (i e are apt to be hyperreactors) Reisner Norman Field and Brown (595) studied 100 male subjects chosen from two medical wards at Bellevue Hospital The prothrombin time was determined before and following a single dose of 100 mg of dicumarol No patient was selected whose prothrombin activity was not normal The pro

desperately ill Fourteen of the patients (70 per cent) had clinically detectable complicating thromboembolic episodes One of these complicated cases represented the only treatment failure (five per cent) in the series of 20 patients

In none of the 19 patients who recovered was there evidence of thrombus propagation once anticoagulation therapy was instituted Furthermore all complicating thromboembolic processes were promptly terminated

In the optimally treated patients the span of bed rest was conspicuously reduced Convalescence was accelerated and the patients were restored more rapidly to their accustomed activity

The gratifying response to this small though representative series of gravely ill patients would seem to indicate that heparin/Pitkin menstruum because of its simplicity of administration prompt effectiveness and absence of toxicity is well suited for the treatment of acute coronary thrombosis and its complications

Long Term Anticoagulant Therapy

Nichol and Borg (593) reported their further experience with long term dicumarol therapy in 68 patients who had suffered one or more attacks of coronary thrombosis and/or myocardial infarction Approximately half the patients had experienced more than one attack previously Thirty six patients on dicumarol had been followed for three to 12 months 20 for one to two years 11 for two to three years and one for five years Prothrombin times are performed at weekly intervals after the patient has become ambulatory and the dosage of dicumarol averages 60 to 75 mgm a day The prothrombin time is maintained at a value twice normal as expressed in seconds the equivalent of a reduction in prothrombin activity to between 10 and 30 per cent of normal Hemorrhage has occurred in one fourth of the patients usually due to the presence of some pathological lesion or to an over dose of dicumarol and has necessitated the abandonment of the therapy in three patients

Nine patients stopped therapy and two of these died later with recurrent attacks Ten patients died while on dicumarol and six were autopsied In two instances there was a fresh coronary thrombosis or infarction in three instances death was ascribed to ventricular fibrillation or congestive heart failure and in one instance

there was cerebral hemorrhage due to rupture of a right ventricular striate artery Of the four patients not autopsied two died of recurrent coronary thrombosis

Of the 49 patients remaining on dicumarol all have been active in business or household duties but four have experienced episodes of acute coronary insufficiency without infarction followed by recovery without complication The patient who had been on dicumarol for five years had three attacks of coronary thrombosis before *dicumarol therapy but none since Many patients comment* upon the abatement of anginal pain while taking dicumarol The authors do not claim that coronary thrombosis can be prevented by this therapy but feel that they have demonstrated that the regime is feasible providing accurate prothrombin determinations can be obtained

Foley (594) has recently summarized and brought up to date the experience which he and Irving Wright had with long term anticoagulant therapy in patients with rheumatic heart disease coronary occlusion and phlebitis migrans Nineteen patients have been maintained on dicumarol without mishap for a minimum of 15 months and some patients have been carried for as long as three years

CONGESTIVE HEART FAILURE

Patients with congestive heart failure are prone to develop thromboembolic complications which increase the morbidity and the mortality of congestive heart failure Kinsey and White (71) reported the presence of pulmonary infarction in no less than 24 of 50 autopsied cases of congestive heart failure Carlotti and his associates (72) in a study of pulmonary embolism in 273 medical cases found that the admission diagnosis in 104 instances had been congestive heart failure

On the other hand patients with liver damage are apt to have a reduced plasma prothrombin activity and to react in an extremely sensitive manner to a given dose of dicumarol (i e are apt to be hyperreactors) Reisner Norman Field and Brown (595) studied 100 male subjects chosen from two medical wards at Bellevue Hospital The prothrombin time was determined before and following a single dose of 100 mg of dicumarol No patient was selected whose prothrombin activity was not normal The pro

thrombin time was determined each day on whole plasma (Link Shapiro technic thromboplastin from ox lung) until it had re turned to normal or until four days had elapsed with no change A barrage of liver function tests were performed on most patients and observation made of the size of the liver the presence or ab sence of ascites and the presence and degree of congestive heart failure

Depression of prothrombin activity to less than 60 per cent of normal occurred in 28 patients of whom 93 per cent had evidence of liver disease or congestive heart failure The patients with the most profound depression of prothrombin activity had extensive liver damage as indicated by the presence of ascites positive cepha lin flocculation tests enlarged livers and/or inverted albumen/ globulin ratios

Among 33 patients with congestive heart failure 14 (42 4 per cent) were hyperreactors as manifested by a depression of pro thrombin activity to below 60 per cent following this single test dose of dicumarol Three of these patients had other liver disease as well Twenty other patients with heart failure (57 6 per cent) of whom three had other liver disease as well did not show a re duction of prothrombin activity to less than 60 per cent in response to the single test dose of dicumarol

The high incidence of congestive heart failure among the pa tients who were hyperreactors to dicumarol is evidence that an en larged liver due to congestive heart failure is physiologically de ranged This is supported by the results of liver function tests It is evident also that the presence of congestive heart failure may alter the patient s response to dicumarol On this basis the authors believe that the response of a patient to a single test dose of dicu marol is a sensitive test of liver function

Wishart and Chapman administered dicumarol to 61 patients with frank congestive heart failure Auricular fibrillation was pres ent in 19 cases (three per cent) and there were definite signs of mitral stenosis in 11 (18 per cent)

In the absence of contraindications and with a normal prelimi nary prothrombin time an initial dose (usually 200 mg) of dicuma rol was given orally In a few cases small doses of heparin were given intramuscularly for the first 24 or 48 hours The prothrom

bin time was determined daily and the dosage of the drug was adjusted to keep the prothrombin concentration between 30 and 10 per cent of normal The average initial prothrombin concentration before dicumarol was started was 62 per cent of normal and in one case it was only 17 per cent evidence that liver function may be significantly impaired in congestive heart failure

The average daily dose of dicumarol for an adequate effect was 78 mg which was considered evidence that patients in cardiac failure require smaller doses of dicumarol than do compensated persons

No hemorrhagic complications developed in any of the cases although it was often necessary to suspend dicumarol therapy because of excessive depression of the prothrombin concentration Vitamin K (30 mg intravenously three or four times daily) was occasionally used to counteract excessive dicumarol effect

The mortality in the series was 32 8 per cent (20 deaths) and autopsies were performed in 12 cases There were no deaths definitely attributable to pulmonary embolism and only 1 death might conceivably have been due to such a condition In the remaining 10 fatal cases death was not sudden and the terminal symptoms were not suggestive of fatal pulmonary embolism No such embolus was found in any of the 12 autopsied cases although small emboli were present in several

The clinical diagnosis of non fatal embolism and infarction in the lungs is difficult and in many cases impossible In this study symptoms and signs of infarction were carefully sought elevations in temperature pulse rate white cell count and sedimentation rate were investigated and x rays of the chest were taken upon the slightest suspicion

Definite pulmonary infarcts developed clinically in 2 patients on dicumarol therapy The dicumarol effect was inadequate before and during the time the embolic phenomena appeared Two patients had transient microscopic hematuria while on dicumarol therapy

At autopsy infarcts (other than myocardial) were present in six out of 12 cases From the ages of the lesions as judged morphologically it was possible to determine that in five cases infarcts had developed either before dicumarol had been given or after it had

been withdrawn In the remaining case pulmonary infarction had apparently occurred in spite of adequate doses of dicumarol

With the clinical and postmortem evidence combined it seems probable that embolic phenomena developed in 4 (6 5 per cent) of the 61 cases despite adequate dicumarol therapy Previously published reports indicate that in a group of comparable cardiac patients one may expect pulmonary emboli in at least 22 per cent

The writers believe that dicumarol therapy is probably effective in protecting the patient with congestive heart failure from the danger of embolism and that controlled anticoagulant therapy may become as important in the treatment of the disorder as it already is in that of thrombophlebitis or of post operative patients although the protection it affords is not absolute

Stats and Davison (597) determined the hypoprothrombinemic effect of a single dose of 150 mg of dicumarol in 48 control subjects and in 36 patients with varying degrees of right sided heart failure Clinical and statistical analysis of the results showed an increased response in those cardiac patients with moderate to severe heart failure There was no difference in the prothrombin time between normal and cardiac patients when whole plasma was used but when 12 5 per cent plasma was used the prothrombin time was prolonged among the patients in heart failure

Multiple Sclerosis

Chiavacci and Putnam (598) surveyed the hypothesis that the characteristic lesions of multiple sclerosis are the result of vascular closure Spotty areas of demyelination with relative preservation of axis cylinders and a purely ectodermal type of repair may be produced by experimental venous obstruction or may be observed in conjunction with a variety of lesions which embarrass the venous return Results of a search for alterations in the capillaries in the nail beds were reported

Observations were made on 48 patients with multiple sclerosis selected from a larger series on the grounds of certainty of diagnosis cooperativeness and convenience For control nine persons employed about the laboratory were observed The authors found that almost all 18 patients (19 men and 29 women) showed altera

tion of the capillaries consisting mainly in spasticity sluggishness or absence of circulation and thickening of intermediate parts of the loop The capillary observations did not correspond with the severity of the patient s clinical condition

These observations seem to point to the primary nature of vascular changes in multiple sclerosis The authors believe that the presence of abnormalities in capillary pattern in association with neurologic signs and symptoms may prove reliable though not infallible evidence in favor of the diagnosis of multiple sclerosis These investigations will be continued on a larger scale with respect to the influence of various chemical and physical agents on the capillary shape

Cox Fantl and Fitzpatrick (599) were prompted by the report of Putnam and his coworkers (49) to administer 3 3′ ethylidene bis-4 hydroxycoumarin (F D C) to 30 unselected patients with disseminated sclerosis Treatment was abandoned in one case after a fortnight but was continued in the remaining patients for periods up to 19 months Treatment was discontinued in 19 patients because of the deterioration of the patient or because of the occurrence of acute exacerbations of the disease

Prothrombin determinations were performed by the one stage method of Quick using plasma from venous or capillary blood Percentages of prothrombin activity were calculated from standardized hyperbolic curves Twenty nine of the 30 patients had a preliminary prothrombin activity between 60 and 100 per cent of normal One patient had a preliminary prothrombin activity between 35 and 40 per cent and was not accepted for treatment

E D C was given orally 0 5 gm for two successive days 0 3 gm on the third day and according to the prothrombin activity thereafter An attempt was made to keep the prothrombin activity between 25 and 30 per cent of normal This was accomplished in 26 patients but in the remaining three the prothrombin activity was not reduced below 50 per cent even on daily doses of 0 3 gm The prothrombin time was determined once or twice weekly depending upon the stability of the patient s response to F D C

No untoward reactions were noted even by patients treated for as long as 12 months and with a total dose of E D C of from 40

been withdrawn In the remaining case pulmonary infarction had apparently occurred in spite of adequate doses of dicumarol

With the clinical and postmortem evidence combined it seems probable that embolic phenomena developed in 1 (6 5 per cent) of the 61 cases despite adequate dicumarol therapy Previously published reports indicate that in a group of comparable cardiac patients one may expect pulmonary emboli in at least 22 per cent

The writers believe that dicumarol therapy is probably effective in protecting the patient with congestive heart failure from the danger of embolism and that controlled anticoagulant therapy may become as important in the treatment of the disorder as it already is in that of thrombophlebitis or of post operative patients although the protection it affords is not absolute

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He states that though he has used anticoagulants in the treatment of cardiac infarctions it is too early to make any statements regarding the results Heparin was also used in a case of transfusion reaction in which there was anuria Two hours after the start of heparin therapy the anuria cleared up and long fibrin casts of tubuli were voided

Finally in fibrinous bronchitis heparin was used to decrease or counteract the deposit of fibrin and when combined with ephedrine and epinephrine is characterized by the author as life saving

CONTRADINDICATIONS AND CAUTIONS IN THE USE OF ANTICOAGULANTS

Hypoprothrombinemia Due to Liver Disease

Hemorrhagic states complicating hepatic disease are generally attributed to hypoprothrombinemia An additional factor in parenchymatous liver disease may be a circulating heparin like anticoagulant Whitesell and Snell (601) emphasize that two additional factors may be associated with a coagulation defect in hepatic disease namely thrombopenia and an increased capillary fragility They reported that not only are thrombocytopenia and increased capillary fragility common in the presence of parenchymatous liver disease *but that there is some correlation between the occurrence* of these defects and an abnormal state of the serum colloids for example an increase in the gamma globulin fraction of the plasma proteins The hazards presented by these findings are the performance of splenectomy for thrombocytopenia of hepatic origin the increased hazard of bleeding at surgery and the danger of postoperative hepatic insufficiency

The increased sensitivity of patients with liver dysfunction including that due to congestive heart failure to dicumarol has been referred to earlier in this chapter Reisner Norman Field and Brown (595) employed single test doses of 100 mg of dicumarol for a liver function test and suggest that 50 mg as employed by Shapiro and his coworkers may have been too small a dose

Unger Weiner and Shapiro (602) have reported further experience with a liver function test of high sensitivity in which they

to 70 gms Twenty five patients were treated for at least several months 12 patients for one year or longer Twenty two patients were studied sufficiently long and well for analysis

Significant exacerbations occurred during therapy in four cases in three whose prothrombin levels were maintained between 20 and 30 per cent and in one at 36 per cent Patients who had suffered frequent attacks of disseminated sclerosis continued to suffer attacks under adequate dicumarol therapy In the group of 11 patients with slowly progressive disease unquestionable deterioration occurred during treatment despite the usual remissions and exacerbations In three of these 11 patients the prothrombin concentrations could not be reduced below 50 per cent or normal

The authors concluded that anticoagulant therapy had no apparent beneficial effect on the course of disseminated sclerosis Comparison of 55 untreated patients observed personally with the results reported by Putnam in his cases treated with dicumarol revealed very similar mean acute exacerbation times—namely 23 24 months as against 27 02 months The reduction of blood prothrombin levels in patients with disseminated sclerosis by means of E D C had no appreciable effect on the course of the disease

Miscellaneous Conditions

Kallner (600) studied patients with pneumonia in whom fever persisted after the pneumonia had been apparently controlled by antibiotic therapy The author used heparin and dicumarol to treat the thrombosis which he feels causes the fever to persist and which he thinks is located in the venous system either of the pelvis or of the lower extremities With this therapy he gives massage* to the lower extremities and permits early movement of the lower extremities and trunk Therapy is continued until the patient is out of bed and moving about freely The same technique is used for suspected thrombotic complications in the treatment of cases of heart disease anemia parturition and elderly patients who have been confined to bed for a long time for any reason and in any cases in which a manifest thrombosis has been present

* Once thrombosis in the lower extremities is diagnosed this seems hazardous to us (C D M I S W)

occur in the winter and spring No other defects of clotting mechanism were known to be of seasonal incidence

The authors tested capillary fragility in 233 healthy children at various times of the year using both positive and negative pressure methods and found that the incidence of increased capillary fragility increased in winter and spring diminished in summer and was minimal in late summer In addition they noted that conjunctival petechiae in the newborn which are supposedly due to rupture of capillaries during labor were most numerous in spring and winter There was thus a distinct parallelism in incidence of cerebral hemorrhage cephalhematoma conjunctival petechiae and excessive capillary fragility

The authors suggest that the use of vitamins K and P during the latter months of pregnancy may prevent these hemorrhagic *tendencies*

Sachs and Labate (604) reported the case of a 23 year old multipara who was admitted in the seventh month of pregnancy with a diagnosis of phlebothrombosis and pulmonary embolism Because of three additional episodes of pulmonary embolism each occurring as the prothrombin time was allowed to approach normal it was necessary to continue dicumarol therapy through the last two months of pregnancy and the postpartum period Intrauterine fetal death occurred on the 53rd hospital day and on the 74th day the woman delivered a stillborn macerated fetus Examination of the fetus revealed that death was due to hemorrhage apparently caused by dicumarol Attention is drawn to the danger of fetal death from hemorrhage which may result from the administration of the drug during the antenatal period

Cotlove Spiro and Vorzimer (605) performed 277 prothrombin determinations at various intervals from early pregnancy through the puerperium on 62 clinic patients using the Link Shapiro method on both whole and 12 5 per cent dilute plasma When the results in the tests of these 62 patients were plotted on a chart there were no significant alterations in the average values nor in the bulk of the specific values when whole plasma was used However using the diluted plasma prothrombin times there was a progressive shortening below the normal range after the third

utilize the response of the prothrombin time following the administration of large doses of vitamin K. The resting level of prothrombin is estimated on 12.5 per cent diluted plasma on each of several consecutive days. Large doses of vitamin K (Synkavite 76 mg.) are given intravenously on each of 4 successive days and the prothrombin time determined on each day following injection.

The results are interpreted as follows: (1) a negative test is one in which the resting level and serial determinations of the prothrombin time are all within normal limits (37 to 42 seconds by the Link-Shapiro technic using 12.5 per cent diluted plasma) or the resting level indicates hypoprothrombinemia which is corrected during the administration of vitamin K, or the resting level is normal and becomes hyperprothrombinemic during the administration of vitamin K. (2) A positive test is indicated by hypoprothrombinemia which remains uncorrected or is exaggerated by the administration of vitamin K, or a normal resting prothrombin time which becomes hypoprothrombinemic during the administration of vitamin K. Forty-five seconds (dilute) has been arbitrarily taken as the dividing line between normal and abnormal, and values within the range of 45 to 47 seconds are considered border line.

Unger, Weiner and Shapiro have found a high degree of correlation between this test and clinical and histological findings and believe it to be a sensitive test of liver function. They recommend its use as a scout test for liver impairment.

Late Pregnancy

In a study of 10,000 newborn children over a period of five years, Kerpel-Fronius, Varga and Pal (603) found a seasonal variation in the incidence of melena, cerebral hemorrhage and cephalhematoma. The peak period was identical for each and occurred during winter and spring with diminution during summer and autumn. Since the trauma of delivery presumably did not have a seasonal variation, an explanation for the incidence variations was sought in possible changes in the clotting mechanisms and in the capillary fragility. The authors state that, according to the literature, the most marked prothrombin reductions have been noted to

CHAPTER 28

The Administration of the Anticoagulants

THE ADMINISTRATION OF HEPARIN

A METHOD for the determination of heparin in blood has been developed by Monkhouse, Stewart and Jaques (606). It is applicable to the estimation of increased quantities of heparin in blood as after intravenous injection or anaphylactic shock. Using the metachromatic method of assay, recoveries of 80-90 per cent were obtained for heparin added to blood in concentrations of 0.2 to 3.6 mg./100 ml., while complete recovery of heparin was obtained from plasma. Normal human blood without added heparin gave a value equivalent to 0.009 mg. per cent of heparin by this method. Owing to the extremely small amounts of heparin thus found in normal blood, certain modifications of the method are indicated in applying it to the estimation of normal blood heparin.

Paritol: A New Heparin-Like Anticoagulant (Heparinoid)

Sorenson, Seifter and Wright (607) have reported observations on the effect in humans of a synthetic anticoagulant prepared by the sulfation of alginic acid. The material is a polysulfuric ester of polyanhydromannuronic acid obtained as a water-soluble sodium salt which is stable at room temperature. Pharmacological data indicate that the drug has about the same toxicity in animals as heparin and is about 1/10 to 1/20 as toxic as other synthetic polysaccharide sulfuric acid ester anticoagulants that have been tested. Rabbits given 5 to 15 mg./kg. of Paritol by intravenous injection every three hours daily for one week showed no toxic manifestations. Studies in animals on the fate of Paritol indicate that about 25 per cent is excreted in the urine. The remainder appears to be inactivated in the blood and the inactivated product picked up by the reticuloendothelial system.

The results reported were based on the administration of Pari-

month of pregnancy and the shortest times appeared in the first few days post partum Values obtained several months post partum were uniformly slightly elevated above normal These statements apply both to average values and to the bulk of the individual values

The authors suggest that among the factors which may play a role in these changes are plasma dilution and concentration alterations in the concentration of fibrinogen and in the prothrombin activator substance Anti thrombins may also play a role In summary the authors state that by the one stage prothrombin determination using 12 5 per cent diluted plasma there is a progressive acceleration of the clotting time beyond the normal range through the course of pregnancy and lasting through the first week post partum At a later post partum period the prothrombin time is somewhat lengthened The results are similar in individual cases in whom serial determinations are made to those in the group as a whole No significant changes are noted when whole plasma is used

vomiting abdominal cramps defecation oppression over the chest pallor sweating bradycardia and fall in blood pressure to imperceptible levels These symptoms and signs responded to prompt administration of epinephrine

One of the other reactions noted was a flushing of the face feeling of epigastric fullness with belching and a 16 mm fall in the diastolic blood pressure These manifestations disappeared without medication when the injection of the drug was discontinued

The third reaction noted was a flushing of the face associated with a 10 mm fall in blood pressure The injection was completed and the flush subsided within 15 minutes Within about two hours both hands were noted to be slightly edematous this lasted about two hours and subsided spontaneously

No toxic effects of Paritol have been observed on the blood kidneys or liver as determined by red blood cell counts white blood cell counts sedimentation rates urine examinations P S P tests prothrombin times B S P tests and cephalin flocculation thymol turbidity and total protein determinations

Further clinical experience with Paritol seems to indicate that it may be a satisfactory substitute for short term heparin therapy Certain reactions are however being studied before final conclusions can be drawn Experience with long term use of Paritol is not yet available

The Administration of Dicumarol

There have been many articles during the past year which have discussed in general terms the administration of dicumarol and the determination of the plasma prothrombin clotting time Olwin (608) Coleman (609) and Blumenthal (610) have written at length upon the control of dicumarol therapy by means of the prothrombin time Wroblewski (611) has emphasized the need for careful laboratory control during dicumarol therapy and has argued in favor of reporting the prothrombin time in seconds

Gastric Acidity and the Absorption of Dicumarol

The extreme variability in the response of the prothrombin time to identical doses of dicumarol has raised the question as to

tol to eleven patients a total of 25 injections It was given intravenously in 1 5 and 10 per cent solutions

The amount of Paritol required to prolong the clotting time two to three times the control time was approximately 5 to 10 mg/kg However some individual variation in response was observed This amount is approximately 13 times that of the sodium

TABLE XIV

METHODS FOR ADMINISTERING THE ANTICOAGULANTS AND POTENTIAL SUBSTITUTES UNDER INVESTIGATION

HEPARIN	
METHODS OF ADMINISTRATION	1 INTRAVENOUSLY
	a Intermittent
	b Continuous
	2 SUBCUTANEOUSLY
	a Pitkin menstruum
	3 INTRAMUSCULARLY
	a Dilute aqueous
	b Concentrated aqueous
	c Oil menstruums
	d Gelatin-dextrose menstruums
POTENTIAL SUBSTITUTES	1 Paritol
DICUMAROL	
METHODS OF ADMINISTRATION	1 Orally
POTENTIAL SUBSTITUTES	1 Tromexan
	2 Phenylindanedione

salt of heparin necessary to produce comparable maximum clotting times The duration of action of 5 to 10 mg/kg given intravenously has been observed to last from four to eight hours but the results suggest that the action may be more prolonged than that of heparin given intravenously

Immediate toxic reactions to the slow intravenous injection of Paritol were observed in three patients one of these was severe two were mild The severe reaction was manifested by nausea

TABLE XV

VARIOUS METHODS AND MODIFICATIONS USED IN DETERMINING PROTHROMBIN AS REPORTED IN THE LITERATURE*

Author(s)	Description	Blood or Plasma	Thromboplastin	Comments
		ONE STAGE METHOD		
Quick, A. J.	Cf. Appendix B	whole plasma	rabbit brain	original one stage method
Stewart and Pohle	Cf. reference 301	whole plasma	rabbit brain	differs in the amount of calcium used
Magath, T. B.	Cf. references 300 & 304	whole plasma	rabbit brain	standardizes thromboplastin before use
Fullerton, H. W.	Cf. reference 430	whole plasma	Russell viper venom	viper venom used as thromboplastin
Link-Shapiro	Cf. Appendix D	12.5 per cent diluted plasma	rabbit lung	use of diluted plasma for greater sensitivity
Brambel, C. E.	Cf. reference 305	whole plasma and 12.5 per cent plasma	rabbit brain	differs in handling of thromboplastin
		BEDSIDE METHODS, ONE-STAGE, USE OF WHOLE BLOOD		
Ziffren, Owen, Hoffman & Smith	*Am. J. Clin. Path., Tech. Sect.*, 4: 13, 1940	whole blood		
Kato, K. & Poncher, H. G.	*J.A.M.A.*, 114: 749-753, March 2, 1940	oxalated capillary blood		
		TWO-STAGE METHOD		
Warner, Brinkhous & Smith	Cf. reference 37	whole plasma	beef lung	requires standardized thrombin solution and fibrinogen
Seegers et al.	Cf. appendix C and reference 614	whole plasma	beef lung	refined method in which Ac globulin is controlled

*Other modifications including both variations and refinements have been used and reported by other workers. These are, however, the more important methods in general use.

Seven patients were studied from the beginning of treatment with dicumarol. Values for Ac globulin were depressed during the first days of dicumarol therapy but had returned to normal by the end of 21 days. Patients treated for longer periods of time (up to 18 months) showed no material variation from normal. The author concludes that factors other than Ac globulin are responsible for

the possible influence of gastric acidity upon the absorption of dicumarol LaTona and LeFevre* have attempted to answer this question by studying the prothrombin response in individuals who were given a standard dosage of dicumarol and determining the amount of free hydrochloric acid present in the gastric contents The amount of free hydrochloric acid was determined by the histamine fractional test and the prothrombin times were determined by a modification of Quick's method Dicumarol was administered to all patients in a dose of 300 mg on the first day and 150 mg on the second day The subjects all of whom but one were postoperative patients were divided into three groups as follows five showed true achlorhydria 10 had at least one fractional specimen from 1 degree through 70 degrees of free hydrochloric acid 17 had more than 70 degrees of free hydrochloric acid

The one consistent finding was the extreme degree of variability in the response of the prothrombin time to dicumarol The data otherwise indicated that there is no correlation between increased or decreased absorption of dicumarol and gastric acidity There was a slight increase in the average prothrombin concentration going from the achlorhydric to the hyperacidity group but the groups showed such a marked variability in response to dicumarol that the authors did not believe this increase to be significant The range of variability in the achlorhydric group was definitely less than in the others There was no correlation between the level of free hydrochloric acid and the prothrombin concentration

One and Two Stage Method for Prothrombin Determination (Table XI)

Olwin (612) states that the two stage method for the determination of prothrombin provides a more accurate and a safer control of prothrombin activity during dicumarol therapy than does the one stage method The latter is of value in estimating a summation of the various factors involved in clotting Prothrombin activity of below 10 per cent by the two stage method does not indicate imminent bleeding especially if the reading by the one stage method is greater than 10 per cent

* LaTona S R & LeFevre F Relationship of dicumarol absorption to gastric free hydrochloric acid *Am Heart J* 38 713 716 (November) 1949

liquid state is highly unstable and that both prothrombin free human and bovine plasmas maintain stability when properly lyophilized and stored at −20 deg C for as long as 10 and 20 weeks respectively The author concludes that these latter plasmas when reconstituted to pH 7 3 are ideal diluents of fresh plasma for the determination of the prothrombin concentration

Deutsch and Gerarde (617) indicated that the prothrombin time of diluted rabbit plasma may be influenced by variations in the fibrinogen level

Simultaneous estimation of the prothrombin time of 12 5 per cent diluted human plasma by the Link Shapiro method and of the fibrinogen concentration of plasma in normal subjects cases of hyperprothrombinemia and in cases of hypoprothrombinemia were performed by Weiner and Shapiro (618) The effect of normal variations of fibrinogen concentration from 180 to 650 mg per cent on the 12 5 per cent diluted plasma prothrombin time in man was not significant The authors point out that massive doses of dicumarol may depress the plasma fibrinogen level but that with therapeutic doses of dicumarol the fibrinogen concentration is maintained within the normal range

Weiner Shapiro Axelrod and Brodie (619) believe that the chief problem involved in dicumarol therapy is that of obtaining an adequate antithrombotic effect without hemorrhage They believe that an understanding of the fate of dicumarol in the body might permit the planning of safer regimens of therapy

The absorption distribution and rate of metabolism of dicumarol was studied The drug is almost completely transformed in the body and only traces are found in the urine after its administration It is transformed slowly with marked variations in different individuals Absorption from the gastro-intestinal tract is slow and varies with the individual and the dose Prothrombin estimations correlated with dicumarol levels show that there is a threshold level for dicumarol below which no prothrombin response is detected Changes in the prothrombin activity lag behind changes in dicumarol levels The magnitude and duration of prothrombin time prolongation correlate much better with dicumarol plasma levels than with the dose of dicumarol administered

the disparity between the results of the one stage and two stage methods

Mawson (613) described modified methods and apparatus for the estimation of prothrombin by the one stage and two stage methods When plasma from patients treated with dicumarol was used the two stage method gave results in fair agreement with those obtained by the one stage method in which Russell Viper Venom *and lecithin were used as thromboplastin* When rabbit brain or ox lung were used as thromboplastin the prothrombin concentration found was lower than that obtained by the two stage method The author discusses possible reasons for this discrepancy and the significance of observations in the control of anticoagulant therapy

Ware and Seegers (614) have described a modified method for *the two stage determination of prothrombin which consists of sup*plying Ac globulin in the form of diluted beef serum for the activation of prothrombin The authors believe that with this modification the two stage procedure becomes a specific quantitative test for prothrombin By comparing the results obtained on a given specimen of human plasma by the original two stage method of Warner Brinkhous and Smith with that determined by this new *modification it is possible to estimate the Ac globulin content of* the plasma When the Ac globulin content of the plasma is below 50 per cent of normal the original two stage method gives considerably lower values than does the modification The modification and the required reagents are described in detail

Schwager and Jaques (615) have also described a simple rapid method for the determination of the prothrombin time using whole blood Thromboplastin dispensed in capillary tubes and stored in a frozen state is placed in the center of a watch glass and 2 cc of venous blood taken in a silicone syringe is added to it The clotting time of the plasma represents the prothrombin time *The authors have used the method for two years with satisfactory* results

Frommeyer (616) has presented experimental data showing that normal human plasma rendered prothrombin free by treatment with barium sulfate and stored at various temperatures in the

hours when doses of 5 to 15 mg/kg had been given in 48 hours following larger doses

Tromexan is more rapidly eliminated than is dicumarol and has therefore a less pronounced effect for any given dose Clinically the initial dose of Tromexan should be about three times that of dicumarol A dose as small as 15 mg/kg has a constant effect on the prothrombin time but to maintain a constant prothrombin level 15 mg/kg is given twice daily Doses as great as 400 mg/kg have been given repeatedly at intervals of several days These were well tolerated and produced curves similar to those obtained with smaller doses Doses of 400 to 500 mg/kg failed to reduce the prothrombin index

$$\left(\frac{\text{Prothrombin time in normal plasma (sec)}}{\text{Prothrombin time of pathic plasma (sec)}} \times 100\right)$$

below 10 No significant untoward effects were noted on the NPN blood sugar bilirubin or blood count The authors conclude that Tromexan presents all of the advantages of dicumarol without the disadvantages of the latter drug

Pulver and von Kaulla (621) found that a considerable amount of a relatively inactive and non toxic metabolic product can be isolated from the urine following the administration of Tromexan They described a method for the quantitative determination of Tromexan in serum and in urine by coupling the drug with diazotized para nitroaniline at pH 6 to form a yellow dye Following separation from the serum proteins Tromexan is extracted with benzene and is measured colorimetrically This method can be applied to other coumarins including dicumarol if standard curves for these are determined The inactive metabolic products of Tromexan are measured also by this method but with concentrations of Tromexan of from 2 to 20 mg/100 cc the method is accurate within ± 15 per cent

Animal experiments in which rabbits were given dicumarol or Tromexan by stomach tube in doses of 50 mg/kg revealed that Tromexan is better tolerated and more rapidly absorbed than is dicumarol The average maximum blood concentration was somewhat less for Tromexan (9 7 mg per cent) than for dicumarol (13 3 mg per cent) but no Tromexan could be demonstrated in

Substitutes for Dicumarol

Tromexan A New Anticoagulant of the Coumarin Series

Several experimental and clinical reports have appeared from Switzerland and England and Czechoslovakia concerning the anti coagulant effect of the ethyl ester of di (4 hydroxy-coumarinyl) acetic acid known as pelentan in Czechoslovakia but as Tromexan in Switzerland and elsewhere This drug is the first member of the coumarin series or for that matter the first drug of any type which gives promise of being a satisfactory substitute

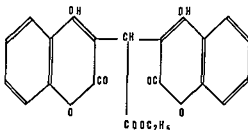


Figure 25

for dicumarol clinically Indeed preliminary reports suggest that it may be a more satisfactory anticoagulant than dicumarol because *of its prompt action and the similarly prompt loss of its effect*

In Switzerland von Kaulla and Pulver (620) reported experimental investigations on mice and on rabbits The single LD 50 for Tromexan was 750 mg/kg in mice (dicumarol LD 50 was 270 mg/kg) and over 1000 mg/kg in rabbits (dicumarol LD 50 was 150 250 mg/kg) Histological studies on mice revealed changes only in the liver and occasionally in the kidneys if 100 mg/kg were administered daily for from 26 to 51 days

Following the administration of a single dose of Tromexan to rabbits they report a prolongation of the prothrombin time was noted after six hours and a *maximum prolongation was attained* in from 24 to 48 hours There was an immediate return of pro thrombin activity thereafter and this reached a maximum in 24

readings of 22 24 seconds at 18 hours and 26 35 seconds depending upon the dose at 24 hours The peak or the greatest prolongations of the prothrombin time from single doses occurred at 36 40 hours returning to normal in from 12 18 hours thereafter

Wright and Burke found that with increased doses Tromexan similarly to dicumarol produced a higher prothrombin time as well as a longer period of hypoprothrombinemia (72 90 hours after initial dose) With doses of 100 to 300 mgs the prothrombin time had returned to normal by the third day (60 72 hours)

Following these experiments which will be reported in detail elsewhere a clinical evaluation of Tromexan was undertaken To date 35 patients have been treated with the drug The following studies are being carried out on each patient before during and after the use of Tromexan daily urine examinations P S P tests B S P determinations cephalin flocculation and thymol turbidity tests RBC WBC and Hbg sedimentation rates the alkaline phosphatase stool studies for guiaic total protein and albumin globulin ratio determinations To date no patient has shown symptomatic or physical evidence of toxicity or any toxicity as evidenced by the above laboratory procedures

The responses to Tromexan have been as follows A satisfactory hypoprothrombinemia is usually obtained following single dose of 1500 mgs Twenty four hours following the administration of a single dose (1500 mgs) of Tromexan the prothrombin time has uniformly reached a level of 26 32 seconds (undilute) and 65 90 seconds (dilute) With single doses of 1200 mgs a lower level was achieved Following a single dose of 1200 1500 mgs the prothrombin time returns to normal in 60 72 hours These results were obtained on both normal controls and patients with thromboembolic disease One patient who was eight months pregnant and who developed thrombophlebitis and one pulmonary embolism was found to be resistant to the drug requiring larger doses than others This phenomenon has been encountered in pregnancy with dicumarol

Patients with thromboembolic diseases including coronary occlusion thrombophlebitis of the lower and upper extremity with and without embolic phenomena were treated An initial dose of 1500 mgs was usually given followed by a maintenance dose of

treatment or who had associated lesions resistant to this treatment Seven patients had had one or several pulmonary emboli before treatment but had no recurrence during treatment There were four recurrences due to insufficient treatment Suspension of treatment must be gradual to avoid the possibility of a hyperprothrombinemic reaction

Della Santa treated four patients with myocardial infarction and six patients with degenerative arterial disorders of the lower extremities of which only one improved Four patients with hemiplegia were treated with delayed but satisfactory remission of the symptoms in one with thrombosis and one with embolism

Wright and Burke* have been carrying out the first studies in the United States on the possible use of the ethyl ester of di (4 hydroxycumarinyl) acetic acid (Tromexan) as a new anticoagulant Because of the enthusiastic reports from the European authors cited above an effort has been made to evaluate this drug

Animal studies were carried out using rabbits and rats The lethal dose in rabbits (3 0 3 5 kg) was found to be over 1200 mg per kg Further toxicological investigation is also being performed by Dr Gruber at Jefferson Medical School

In the work of Wright and Burke because of species and individual variations in response to anticoagulants the rabbits were standardized with a 3 0 mg dose of dicumarol according to the technic of Link Campbell and Overman Resistant animals were eliminated To the sensitive animals a NaOH solution of Tromexan was fed by tube in doses of 100 200 300 400 500 600 mg Prothrombin determinations (Link Shapiro) were done at six hour intervals around the clock for the first twenty four hours and thence every 12 hours No changes were noted in six hours Inconsistent elevations in the dilute prothrombin time were evident at the end of twelve hours while at 18 and 24 hours the undilute and dilute tests showed consistent and reproducible prolongation of the prothrombin time with doses of 1200 1500 mg The normal time (10 12 seconds undilute) was doubled in 18 24 hours with

* Wright I S & Burke G E Tromexan the Ethyl Ester of di (4 hydroxy cumarinyl) Acetic Acid Its Anticoagulant Properties Presented before the *Course on Diseases of Blood Vessels* American College of Physicians March 16 1950

after pregnancy In all these cases doses of 10 to 20 mg/kilo yielded a very constant decrease of prothrombin level The decrease began earlier than with dicumarol about the 12th hour and the full effect was obtained between the 24th and the 48th hour Return to a normal level was quite constant and 100 per cent prothrombin was reached by about the 96th hour

This constancy is very different from that observed with dicumarol Individual susceptibility to the drug seems also to be less important than in the case of dicumarol

P I D was given to two patients with known thrombophlebitis 10 mg/kg every three days This dose was effective in controlling the prothrombin level around 30 per cent The patients state was in both cases favorably affected In the 41 cases where the drug was given prophylactically no phlebitis was observed

In contrast with these advantages the complete inactivity of vitamin K_2 even in huge doses and even when given prior to the administration of P I D must be emphasized

The effect of P I D on prothrombin time was tested by Jaques Taylor and Lepp (626) in dogs and rabbits Single doses showed a rapid but slight effect on prothrombin time Repeated administration of the drug at frequent intervals caused a marked effect on the prothrombin time 8 3 mg/kg every eight hours gave a prothrombin time of infinity 1 mg/kg every eight hours doubled the prothrombin time Withdrawal of P I D caused the prothrombin time to return to normal within 36 hours Vitamin K had no effect on the action of P I D

The prolonged prothrombin time following administration of P I D was accompanied by a very marked diminution in Factor V activity (Owren) P I D itself had little effect on the components of the clotting system Large doses of the drug over a long period of time plus other factors produced a hemorrhagic condition similar to that of dicumarol overdosage Withdrawal of the drug rapidly reversed this condition No toxic effects were observed with 8 3 mg/kg given every eight hours for 18 days to dogs The P I D was excreted by the kidneys

A study was made by Mentzer (627) to determine the relation between the chemical structure of various compounds similar to dicumarol and their anticoagulant activity His conclusions are

600 900 mgs once a day Little variation has been found in repeated prothrombin times following a single daily dose and these workers feel that divided doses may not be necessary

As yet no definite statement may be made as to the ease of regulation of a patient on Tromexan as compared with dicumarol It would appear on the basis of these studies that because of its more rapid action the results of a dose may be evaluated the following day It should be emphasized that unless the prothrombin time is too prolonged daily dosage is important for if the dose is missed for one day the time will return to normal within 48 hours At the same time the rapid excretion of this drug reduces the danger of hemorrhagic complications

The results reported from abroad and as experienced by Wright and Burke in this country appeared to be encouraging Tromexan appears to have certain advantages over dicumarol as outlined above A more complete evaluation of this substance is being undertaken by the Committee on Anticoagulants of the American Heart Association

Phenylindanedione (PID) A Prothrombinopenic Agent

Meunier Mentzer and Molhe (624) reported that 2 phenyl in dane dione 1 3 (P I D) is a more rapidly acting prothrombinopenic agent than dicumarol

*Soulier and Gueguan (625) studied the effect of this drug experi*mentally on the rabbit and clinically in humans

In the first series of experiments using 16 rabbits the authors found that phenyl indane dione (P I D) had a marked effect on the prothrombin level Doses of 10 to 20 milligrams per kilo produced a decrease of prothrombin to a level of 30 to 40 per cent this effect being reached before the eighhteenth hour There was no modification of platelets clot retraction or fibrinogen level Higher dosage did not produce greater hypoprothrombinemia and the authors did not find any hemorrhages even with a dosage ten times the standard dosage The lethal dose was well over 600 mg/kilo which gave a very high margin of safety Histologic examinations of the rabbits given very high doses of P I D (under 400 mg/kilo) did not show histologic injuries

P I D was used in the prevention of thrombosis in 13 women

CHAPTER 29

Hemorrhage Due to the Anticoagulants and Its Management

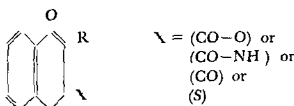
HEMORRHAGE DUE TO HEPARIN

Protamine (Salmine) and Toluidine Blue

IN A STUDY of the toxicity of the protamine salmine Jaques (628) confirmed the fact that among the more common experimental animals protamine is most toxic to the dog. Not only is protamine toxic to the dog at a much lower dose level but is unusual in the nature of its toxic effects. The intravenous injection of salmine in the dog caused a pronounced fall of blood pressure with rapid recovery the result of an extensive vasodilatation in the arterioles of muscles. There was a definite transient thrombocytopenia and leukopenia. Salmine added to blood in silicone treated containers caused thrombocytopenia but not leukopenia. The author concludes that it is unlikely that protamine will be toxic clinically.

Parkin and Kvale (629) found that 1.5 mg. of salmine sulfate neutralized 1 mg. of heparin in vitro. When salmine sulfate was administered in large doses to guinea pigs, rabbits and dogs, it was found to have toxic effects but when small doses such as 1.0 mg. per kg. of body weight were administered, toxic effects were not noted. Salmine neutralized the anticoagulant effect of intravenous injections of heparin into dogs. When heparin in Pitkin's menstruum was injected intramuscularly into dogs the elevated coagulation time returned to normal temporarily after the intravenous injection of salmine. The authors also reported studies of 10 persons who underwent tests with salmine sulfate. They found that in human subjects the intravenous injection of 10 to 50 mg. of salmine sulfate neutralized promptly the anticoagulant effect of 50 mg. of heparin. When salmine sulfate was administered slowly in these doses it did not produce any reactions.

similar to those of Link and his collaborators but whereas the American authors believe that the B cycle is necessarily an hydroxy 4 pyrone 1 2 Mentzer estimates that other cycles such as thyo pyrone quinon pyridin cyclo pentanedione are able to confer to the molecule the same activity as the B pyronic cycle In conclusion all the active compounds have the same structure which can be schematized as follows



If R is an atom of chloride or of hydrogen or a complex of at least six carbon atoms the molecule behaves as an antivitamin K All the compounds also have in common the O atom in B this O atom can belong to an enolic or ketonic group but the blockage of this oxyhydrile function suppresses the activity

these patients the hemorrhagic complication responded permanently to toluidine or to protamine

Patients with malignant blood diseases associated with hemorrhage and with increased protamine titration and whole blood clotting times gave a variable response to toluidine blue therapy Difficulty in controlling local hemorrhage appeared to be due to the impaired formation of platelet thrombi which appeared to be unaffected by toluidine or protamine

When bleeding was uncomplicated as in menorrhagia or post partum hemorrhage intramuscular protamine gave results equal to or better than the dye In bleeding associated with serious marrow disorders toluidine blue was more effective Protamine sulfate is rapid in action the action of toluidine is slower but more prolonged Combined therapy was used occasionally

Fifty mg of protamine sulfate was administered intramuscularly in 5 cc aqueous solution every four to six hours Usually 150 mg protamine was given intravenously in saline over a period of one hour simultaneous with the first intramuscular dose

The dosage range for toluidine blue varied considerably Current practice is to give 6 to 8 mg per kg of body weight daily for three days and one half this dose daily for three days thereafter Bleeding recurs commonly if any less vigorous program is followed The dye is dissolved in isotonic sodium chloride solution passed through a Seitz filter and administered slowly over a period of two hours

The only reaction to protamine injected intramuscularly is occasional local pain When toluidine blue is injected intravenously about 15 per cent of patients experience transient nausea and vomiting A slight but transient blue tint to the skin has been noted in anemic patients

The nature of the clotting defect in the patients reported appears to be heparinlike but is probably not identical with that produced by the intravenous injection of commercial beef heparin Only occasionally could an anticoagulant effect be demonstrated in the blood of these patients The exact nature of the deranged clotting mechanism in these patients is not known at this time

Toluidine blue is of genuine value as an antihemorrhagic agent

Allen et al (630) reported data on a series of patients with spontaneous bleeding who exhibited a clotting defect characterized by an increase in the protamine titration and frequently a prolongation in the clotting time of the whole blood Many of these patients had a moderate or severe thrombopenia The nature of the defect revealed by the protamine titration resembles but is not identical with that produced by the intravenous injection of commercial beef heparin it may be influenced by factors other than heparin and is probably increased by a disturbance which interferes with fibrin formation

The blood of these patients showed an increased protamine titration when the prothrombin level was normal or near normal when fibrinogen levels were not abnormal and when fibrinolysin was not grossly disturbed Many patients had thrombopenia but this was an associated disturbance independent of the protamine titration Rarely was the clotting time of whole blood of these patients sufficiently prolonged to indicate an appreciable delay in the clotting of normal blood

The bleeding of many of these patients appeared to respond to the administration of toluidine blue and/or protamine sulfate The following observations were made on each patient clotting time of whole blood protamine titration erythrocyte leukocyte and thrombocyte counts measurement of prothrombin activity and gross observation of clot retraction and fibrinolysin

The protamine titration was increased in all of these patients even though some did not respond to toluidine blue or protamine sulfate *In some the increased protamine titration was due to* hemophilia in others to pronounced prothrombin deficiency Neither of these groups responded to toluidine or to protamine Patients who did respond had neither hemophilia or prothrombin deficiency but did have an increased protamine titer It is obvious that each patient with a bleeding tendency must be studied carefully if therapy is to be applied correctly

Hemorrhagic episodes occurred in some patients at times when severe endocrine disturbances are known to occur which suggested that there may have been a relationship between the bleeding and endocrine disturbances especially in the estrogens In

tions in a small drop of medium containing the disodium salt of dicumarol in 10 per cent rabbit serum and Tyrodes solution were sealed into deep well micro culture slides and incubated at 38° C After 48 to 72 hours the preparations were fixed in Bouin s solution washed repeatedly stained and mounted

All of the control cultures of liver showed proliferation of endothelial like cells at 48 and 72 hours In concentrations of dicumarol of 1 50 000 and 1 100 000 the cultures contained living cells at the end of 48 to 72 hours In concentrations of dicumarol of 1 10 000 proliferating cells were present after 48 hours but these died and disintegrated in those cultures observed for 72 hours Spleen cultures contained proliferating blood cells in media containing dicumarol in concentrations of 1 50 000 and 1 10 000 in 48 and 72 hours

Thus concentrations of dicumarol of 1 100 000 and 1 50 000 did not inhibit the proliferation of endothelial cells when compared with controls after 48 and 72 hours 1 10 000 concentrations of dicumarol produced death and lysis of proliferating cells in liver culture after 48 and before 72 hours but not in spleen cultures

One hundred patients receiving dicumarol were studied by Jubelirer and Glueck (633) to determine if any correlation existed between the occurrence of hemorrhage and increased capillary fragility as measured by the Gothlin test Six of these patients had received dicumarol continuously the shortest period was three months and the longest 19 months None of these patients demonstrated a positive Gothlin test Hemorrhage was observed seven times in 100 cases of patients receiving dicumarol In none of these was the Gothlin index positive Seven patients demonstrated a positive Gothlin test who gave no clinical evidence of hemorrhage

A discussion of the interpretation of the various tests for the detection of increased capillary fragility was followed by a review of the pathologic findings of hemorrhage occurring with dicumarol This study suggests that the status of the cutaneous capillaries as detected by the Gothlin test does not reflect alterations which may occur in other portions of the capillary bed Careful clinical observation and meticulous laboratory control are necessary to detect and prevent hemorrhage in patients receiving dicumarol

in some instances of hemorrhage uncontrolled by other methods In malignant conditions bleeding tends to recur unless toluidine blue is administered at regular intervals In patients with leukemia and treated with aminopterin the problem is complex Aminopterin can produce bleeding and an increased protamine titration in the normal animal It also may induce an enteritis with focal bleeding When this is complicated by thrombopenia secondary to acute leukemia only healing of the local areas will control the gastrointestinal bleeding

Toluidine blue does not influence the bleeding in uncomplicated idiopathic thrombopenia unless there is an associated increased protamine titration

The correlation between clinical response and improved protamine titration has been striking To date the protamine titration has proved to be the best guide for estimating progress in this type of hemorrhagic disorder

Holoubek Hendrick and Hollis (631) reported three cases where toluidine blue was used to treat bleeding in patients with thrombocytopenia There was little or no response to the dye in one case but a dramatic response followed the administration of the dye in the two other cases Heparin titrations performed on one of the latter patients showed an increased heparin like activity The authors suggest the following indications for therapy with the antiheparin drugs (1) petechial bleeding in selected patients with thrombocytopenia (2) in preparation for splenectomy in patients with thrombocytopenic purpura (3) in instances of acute bone marrow suppression and (4) for decreasing the amount of petechial and oral bleeding from patients with leukemia Toluidine blue will also counteract bleeding tendency in patients given too much heparin Toluidine blue titrations performed on 30 patients with purpuric states associated with thrombocytopenia revealed a positive test *in all instances of leukemia*

Hemorrhage Due to Dicumarol

(See also footnote on page 308)

The Toxicity of Dicumarol

Goldstein and Cameron (632) observed the effect of various concentrations of the sodium salt of dicumarol on isolated sections of liver and spleen *from 11 day chick embryos* Cultures of these sec

Within 24 hours after hospitalization multiple cutaneous and subcutaneous petechial hemorrhages had appeared with melena and a huge sublingual hematoma The hematoma caused the tongue to swell to the size of a tangerine threatening to obstruct the patient s airway The process was not stopped by blood trans fusion A tracheotomy was performed A submandibular hematoma formed and the patient was considered in extremis 1000 cc of stored blood was given intravenously and vitamin K was given intramuscularly without improvement 1500 cc of fresh blood was then given over a period of 48 hours with prompt and dra matic improvement This case illustrates the hazard of administer ing dicumarol without laboratory control the need for using fresh blood to counteract the effect of dicumarol and the in effectiveness of vitamin K unless given intravenously in large doses

Young Derbyshire and Cramer (636) found 40 confirmed cases of paradoxical embolism in the literature 33 due to auricular and seven to ventricular septal defects Fifty per cent of the emboli were cerebral

They reported a case of a 50 year old woman who bled severely from the incision 24 hours following a hysterectomy Her pro thrombin time was found to be 27 minutes and *it was subsequently determined that she had taken 950 gm of dicumarol prescribed by an osteopath during the week before operation* She was given blood transfusion and vitamin K

The patient s hematomata became infected and five weeks post operatively she suffered a sudden pain in the chest One week later she suffered emboli to the right leg and to the left arm and died 12 hours later

At necropsy there was thrombosis of the right hypogastric vein and pulmonary embolism Other emboli had passed through a patent auricular septum (due to rise of right auricular pressure) to the systemic circulation An embolus was found lodged in the foramen ovale

Applebaum and Shulman (637) reported an instance of the indiscriminate use of dicumarol where facilities for the determina tion of the prothrombin time were not employed A 55 year old white male was told by his physician that he had a clot on the heart and was given dicumarol He took 300 mg on the first day

Instances of Hemorrhage

The uncontrolled or inadequately controlled administration of dicumarol continues to be the single most common cause for the hemorrhagic complications of dicumarol therapy Lack of adequate laboratory control *is one of the most important factors op*erating in the occurrence of bleeding in this type of therapy To our personal knowledge many instances of bleeding during the administration of dicumarol are unreported and some of these are undoubtedly serious

Duff and Shull (634) reviewed the reports of 21 deaths attributed to dicumarol and added two previously unreported cases They *comment that a significant number of fatalities have occurred in* patients with subacute bacterial endocarditis (seven of the 23 fatalities) death being due usually to hemorrhage into the brain A significant number of deaths has followed massive hemorrhage into the gastrointestinal tract from a surgical wound or a benign or malignant ulceration The authors have observed two fatalities both due to cerebrovascular accidents occurring at the time the prothrombin time was prolonged excessively

They emphasize the need for proper laboratory control of dicumarol therapy and bewail those instances of fatal hemorrhage from dicumarol in which the prothrombin time was not followed during the course of therapy They note also that the use of Russell viper venom as thromboplastin may fail to demonstrate moderate prolongations of the prothrombin time which are revealed by Quick s method

Duff and Shull conclude that *the most important of all contraindications to the use of dicumarol is lack of reliable laboratory facilities* for prothrombin determination The drug should be administered with caution to patients with severe hypertension especially if there is a history of cerebrovascular accidents

Miller and Drucquer (635) reported the case of a 57 year old male who entered the hospital with severe hematuria The cause for this hematuria was not known until a detailed history had been taken during which interval other hemorrhagic symptoms had appeared *The patient had ingested 100 mg of dicumarol daily on his own initiative* for a period of nine to 10 days After seven days he had experienced abdominal pain and twenty four hours later hematuria had appeared

Within 24 hours after hospitalization multiple cutaneous and subcutaneous petechial hemorrhages had appeared with melena and a huge sublingual hematoma The hematoma caused the tongue to swell to the size of a tangerine threatening to obstruct the patient s airway The process was not stopped by blood transfusion A tracheotomy was performed A submandibular hematoma formed and the patient was considered in extremis 1000 cc of stored blood was given intravenously and vitamin K was given intramuscularly without improvement 1500 cc of fresh blood was then given over a period of 48 hours with prompt and dramatic improvement This case illustrates the hazard of administering dicumarol without laboratory control the need for using fresh blood to counteract the effect of dicumarol and the ineffectiveness of vitamin K unless given intravenously in large doses

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and 100 mg a day thereafter Four or five days before hospital admission the patient noted that his urine was dark and on the day prior to admission he suffered severe bilateral lower quadrant and lumbar back pain He entered the hospital acutely ill three weeks after the onset of his illness

Upon hospital entry the patient presented a boardlike abdomen and tenderness in the flanks and costovertebral angles His bleeding time was 55 minutes and no clot formed after 20 minutes The prothrombin time by the Smith bedside method was five minutes and 54 seconds His urine was port wine in color and filled with erythrocytes At least 1800 mg of dicumarol had been ingested

The patient was given 60 mg of Synkavite intravenously and one pint of blood by transfusion Recovery was prompt The urine was clear after the sixth day Stools were never grossly bloody Some hemorrhages were seen on the skin on the day after admission

Hammarsten (638) has reported the case of a 58 year old white male who suffered an acute myocardial infarction one hour after the injection of 1 cc pitressin during the course of cholecystography Preliminary prothrombin times were 14 1 seconds (prothrombin activity 78 per cent of normal) and 16 5 seconds (prothrombin activity 55 per cent of normal) Dicumarol was given in moderate doses since the patient proved to be more sensitive to the drug than usual On several occasions the prothrombin activity fell to 10 per cent of normal or less No bleeding occurred and no vitamin K was given Liver function tests indicated impaired hepatic function

On the 23rd day of dicumarol therapy the patient died in acute heart failure At autopsy the pericardium contained 800 cc of dark red blood A thin walled aneurysmal dilatation existed on the anterolateral surface of the left ventricle An endocardial thrombus lined the aneurysmal dilatation There was an occlusion of the anterior descending branch of the left coronary artery No gross laceration and no minute rupture of the ventricle nor of the coronary vessels could be identified

The author comments that the majority of cases with hemopericardium secondary to myocardial infarction are associated with

complete rupture of the wall of the heart The gradual onset of symptoms of cardiac tamponade in this patient indicates that the bleeding occurred slowly Undoubtedly the anticoagulant therapy made possible the massive hemorrhage

Koller and Pedrazzini (639) reported that an elderly woman with thrombosis of the central vein of the left retina for whom dicumarol had been prescribed ingested 300 mg of the drug daily for 14 days *without a single determination of the prothrombin time* A severe hemorrhagic diathesis developed and the patient s condition was precarious for one week despite adequate treatment There was rapid improvement after 10 days and gradual complete recovery It is surprising that with this dosage the hemorrhages did not appear for two weeks

The coagulation time of the whole blood was not increased (Lee White method) Vitamin K did not cause the prothrombin time to return to normal and this occurred only after 15 days during which multiple transfusions were given There was increased capillary permeability as demonstrated by a strongly positive Rumpel s phenomenon and by the flourescein test of the capillaries of the iris The usual liver tests were normal

Recently one of us (I S W) saw a patient who was directed to take 150 mg of dicumarol a day for anginal pain by a physician who (a) did not do a single prothrombin test (b) did not mention any risk or danger to the patient (c) went on a vacation After approximately three weeks the patient developed massive subcutaneous purpera from head to feet By the use of massive repeated fresh whole blood transfusions and three daily doses of 1000 mg each of vitamin K_1 oxide she recovered Such treatment is difficult to defend in the light of the voluminous literature on this subject

The Treatment of Hemorrhage and of Excessive Hypoprothrombinemia Due to Dicumarol

The Use of Blood Transfusions

According to Schilling Natale and Amill (640) the prothrombin activity of stored blood is increased through the first four or five days is normal from the fifth through the seventh day and falls slowly thereafter to slightly less than 50 per cent of normal by the

21st day The initial increase in *prothrombin activity is thought* due to the disintegration of platelets and the liberation of thromboplastin The authors conclude that it is practical to use banked blood to treat hypopropthrombinemia or *bleeding secondary* thereto during the first week of storage

Vitamin K_1 Oxide

James Bennett Scheinberg and Butler (641) gave 101 patients dicumarol in daily oral doses of 300 mg the first day and 200 mg on each successive day until the prothrombin activity was less than 20 per cent of normal The patient was then either allowed to recover untreated or given large single doses of Hykinone Synkavite or vitamin K_1 oxide The efficiency of these substances was estimated by (1) the time elapsing between administration of the drug and the conversion of pronounced to moderate hypoprothrombinemia and (2) the time elapsing after administration of the agent until the appearance of a prothrombin level consistent with normal intravascular clotting Vitamin K_1 oxide was strikingly more effective in both respects

Among 26 patients given 0 5 gm or more of vitamin K_1 oxide intravenously the prothrombin time was shortened and remained at a value representing not less than 30 per cent of normal on an average of 13 hours When menadione sodium bisulfite (64 to 180 mg) was given intravenously to 19 patients this shortening of the prothrombin time was achieved on an average of 4 7 days When Synkavite (100 to 500 mg) was given intravenously to six patients an average time of 5 3 days elapsed Six patients with severe hypoprothrombinemia who were treated with 0 1 gm or more of vitamin K_1 oxide required an average *of four hours to achieve a pro*thrombin concentration within what is generally regarded as a safe range

About one of every five patients required five or more days to achieve a significant therapeutic effect from dicumarol in the usual doses The requirement of an individual subject for dicu*marol* is approximately predictable on the basis of the degree of his previous responsiveness to the drug An exception to this situation occurs shortly after the administration of vitamin K_1 oxide after which patients are relatively insensitive to dicumarol

Miscellaneous Observations on Vitamin K and Related Compounds

Quick and Stefanini (642) described a simple vitamin K free diet which produces a marked hypoprothrombinemia in newly hatched chicks within 10 days They also outline a method for vitamin K assay

It was noted that 1 5 to 2 gammas of 2 methyl 1 4 naphthoquinone or slightly more than 2 5 gammas of natural vitamin K_1 per day was required to maintain the prothrombin levels of chicks during the first ten days of life The injection of menadione into markedly deficient chicks caused the prothrombin activity to return slowly at first then progressively more rapidly gradually becoming normal after four hours The size of the dose beyond that minimally effective did not influence the speed of recovery of prothrombin activity

The susceptibility of chicks to the action of dicumarol was increased by removal of vitamin K from the diet The addition of vitamin K counteracted the hypoprothrombinemia No difference was noted between the efficacy of natural vitamin K and menadione Excessive intake of vitamin A which causes hypoprothrombinemia in rats had no effect on the prothrombin level of chicks receiving vitamin K

Boyd and Warner (643) studied the prothrombin level in rats treated with dicumarol by the two stage method There was a considerable variation from day to day in the prothrombin level but a definite recovery phase was apparent soon after the initial fall in prothrombin caused by dicumarol Later the animals showed a definite tendency to escape from the effect of the drug

Menadione in doses of 50 mg daily by stomach tube and menadione bisulfite (Hykinone) in doses of 4 cc (10 mg menadione) daily by intraperitoneal injection had no detectable effect on the prothrombin level of rats whether given before during or after dicumarol administration This is in keeping with clinical experience which shows that vitamin K preparations must be given intravenously and in large doses to be effective in counteracting the hypoprothrombinemia due to dicumarol

To determine the possible influence of vitamin P compounds

on the anticoagulant effect of dicumarol Martin and Swayne (644) used rats according to the technique of Overman et al The chemicals under test were mixed with cottonseed oil and were given orally on three successive days to five rats in each series The prothrombin times were determined four hours after the last dose Dosages were as follows dicumarol 10 mg /kg vitamin P compound 80 mg /kg ascorbic acid 80 mg /kg menadione 3 2 mg /kg

The authors conclude from their findings that (1) D-catechin and rutin counteract dicumarol while hesperidin does not and (2) ascorbic acid counteracts dicumarol and acts synergistically with d catechin in this respect

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The serious hazards of anticoagulant therapy are emphasized by the report of Lilly and Lee (Lilly G D & Lee R M Complications of anticoagulant therapy *Surgery* 26 957 969 (December) 1949) The experience of others has not been so discouraging as demonstrated by the comment made by G H Pratt in reference to this paper (Pratt G E Classification and treatment of the varicose post thrombotic and arterial venous problems *Bull N Y Acad Med* 26 306 328 (May) 1950

CHAPTER 30

Failures and Abuses of Anticoagulant Therapy

ARTZ Martin and McCleery (645) have summarized some of the observed inadequacies of dicumarol therapy in the treatment of venous thrombosis as follows

1 The frequently unpredictable response of the patient makes it difficult to maintain the prothrombin level within the therapeutic range of 10 to 30 per cent of normal
2 Thrombosis may occur even when the prothrombin depression is maintained within the therapeutic range
3 Thrombosis may extend despite a hypoprothrombinemia of less than 30 per cent of normal
4 A transfusion of whole blood to rectify an excessive depression of prothrombin activity may increase the coagulability of the blood sufficiently to permit the occurrence of thromboembolism
5 The prothrombin determination by the one stage method may be inaccurate if performed on blood containing even moderate amounts of heparin

The authors suggest that the newer preparations of heparin in gelatin menstruums may prove safer and more dependable than dicumarol

It should rightly be mentioned that (a) the therapeutic level of a clotting time cannot always be maintained during heparin administration (b) emboli and thromboses have occurred during supposedly therapeutic levels of heparin therapy (c) heparin therapy is vastly more expensive and (d) long term ambulatory therapy is not practical with heparin (I S W & C D M)

Hypercoagulability of the Blood

Hyperprothrombinemia

Sandrock and Mahoney (646) noted that a definite increase in prothrombin activity of whole plasma the second or third post operative day appears to be a warning of impending venous throm

bosis Using a one stage method for determining the prothrombin activity they studied 382 surgical patients of many types post operatively Thrombosis did not develop in any patient studied the first second or third postoperative days who had not had preceding hyperprothrombinemia

Neither postoperative hyperprothrombinemia nor thromboembolic complications developed in 306 patients Thrombosis developed in 16 Dicumarol was administered prophylactically to 41 patients being started in 18 immediately after operation and in 23 on the third postoperative day because of a sudden rise in the whole plasma prothrombin activity on that day Because of inadequate dicumarol therapy one patient had a nonfatal pulmonary embolus 12 days postoperatively None of the other patients given dicumarol had thromboembolic complications Nineteen patients had hyperprothrombinemia the third postoperative day but clinical evidence of thrombosis did not develop Unexplained tachycardia and fever developed in 10 of this group during the post operative period

The authors concluded that all patients showing hyperprothrombinemia the second or third postoperative day should receive dicumarol prophylaxis unless there are definite contraindications It is not necessary to reduce prothrombin concentration to dangerously low levels when dicumarol is being used prophylactically Hyperprothrombinemia occurs before thrombosis can be diagnosed by clinical examination When thrombosis is established prothrombin activity may be normal or even subnormal

Heparin Tolerance Tests

Kravchick & Sheiman (617) studied the Silverman modification of the Waugh Ruddick in vitro heparin tolerance test as a method for predicting thromboembolism in patients Seventy four controls 12 obstetrical patients and seven postprostatectomy patients were studied Statistically the results failed to show a significant difference between the control and the post partum and postoperative groups

Fowler (648) studied 29 postoperative patients and three patients with acute thrombophlebitis by means of the following six tests

which were run simultaneously and then repeated on seven of the postoperative patients later in their postoperative courses (1) modified Lee White clotting test (2) the lusteroid tube coagulation test (3) the prothrombin times on whole and (4) on 12 5 per cent plasma (5) the Waugh Ruddick heparin retarded coagulation test and (6) the heparin tolerance test Twenty seven patients with congestive heart failure were studied by the lusteroid tube coagulation test and by the modified Lee White test Fifty control patients were studied by the lusteroid tube coagulation test and the modified Lee White test while 20 control patients were studied with the heparin tolerance test and the modified Lee White test The whole and dilute prothrombin times were studied on 28 control patients and the Waugh Ruddick test by 25 determinations on 15 control subjects

Of 29 postoperative patients studied evidence for accelerated coagulation was obtained as follows 19 by the Waugh Ruddick test 10 by the lusteroid tube coagulation test six by increased heparin tolerance five by shortening of the prothrombin time of whole plasma three by shortening of the prothrombin time of 12 5 per cent diluted plasma and three by the modified Lee White test The same tests repeated on seven patients showed persistence of hypercoagulability on the 12th post operative day However the different tests did not correlate and the only patient who subsequently developed thrombophlebitis was normal in respect to all tests Three other patients with thrombophlebitis showed accelerated coagulation in lusteroid tubes and shortening of the prothrombin time with whole plasma but gave normal responses to the Waugh Ruddick test and to the dilute plasma prothrombin time Of 27 patients with congestive heart failure only one showed accelerated clotting in lusteroid tubes and two showed accelerated clotting by the Lee White test

Fowler concluded that hypercoagulability of the blood is a frequent finding postoperatively for as long as 12 days following operation The poor correlation obtained between the various clotting tests suggests that they are concerned with different factors involved in clotting They did not permit the prediction of which postoperative patients are going to develop venous thrombosis

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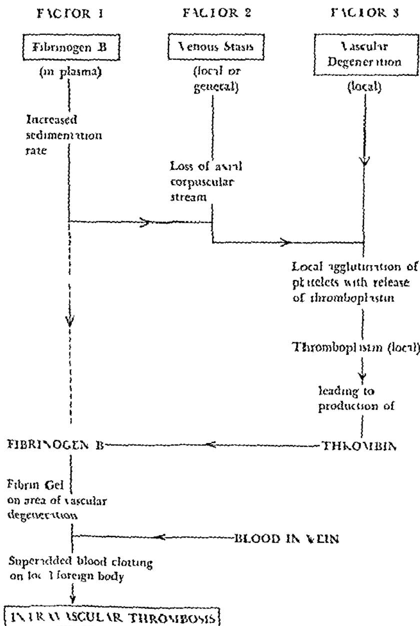
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TABLE XVI

THE PATHOLOGY OF INTRAVASCULAR THROMBOSIS
(After H Cumminge M J Australia 1 31 March 12 1919)



When performing the heparin tolerance test blood for analysis should be withdrawn from a vein other than that into which the heparin is injected Of the tests studied the author found the Waugh Ruddick test the most sensitive but its lack of specificity indicates that it is of no value in predicting or diagnosing thrombophlebitis

Fibrinogen B

Lyons and Cumminge (649) have studied in detail the role of fibrinogen in thromboembolism Lyons described a form of fibrinogen which he termed fibrinogen B as an intermediate stage between normally occurring plasma fibrinogen and fibrin He contends that an increase in the amount of this form of *fibrinogen in the blood is an important factor in the development* of thromboembolic phenomena postoperatively and postpartum According to Lyons and Cumminge intravascular clotting is the *end result of three factors—the presence of fibrinogen B in the* plasma localized or generalized venous stasis and traumatic infective or degenerative endothelial changes in the vessel wall *These factors are shown in their respective roles in the accompanying* schema adapted from Cumminge (Table XVI)

Lyons and Cumminge have found that in cases where little or no *fibrinogen B develops after operation thrombosis* does not occur except in localized varicosities in the presence of intravenous cannulation or in extensions of existing venous or pulmonary thrombosis The authors feel that the fibrinogen B determination has both prophylactic and prognostic value They claim that postoperatively and postpartum serial fibrinogen B determinations will either remain negative in which case thromboembolism almost never occurs (except under the circumstances described above or will show a development of fibrinogen B commonly by the second week Cumminge uses heparin postoperatively under any one of the following circumstances (1) confinement to bed (venous stasis) (2) pyrexia (especially of low grade intermittent nature) (3) accelerated blood coagulation time (three to five minutes) or (4) presence of *fibrinogen B in more than* slight amounts

After thrombosis serial fibrinogen B findings may be one of

time was determined every day or every second day on patients receiving dicumarol and the blood volume was determined only after admission and just prior to discharge

The Waugh Ruddick test was performed 138 times on 31 patients A high percentage of irregular curves was obtained At the time of admission the curves were normal in 20 patients (64 5 per cent) low (increased tendency to clot) in six patients (19 4 per cent) and high (decreased tendency to clot) in five instances (16 1 per cent) Thus upon admission in seven cases only (22 6 per cent) was there an increased tendency toward clotting a finding at variance with those of Ogura et al (378) During hospitalization only two of 14 patients not receiving dicumarol showed an increased clotting time the majority remaining unchanged In those patients receiving dicumarol two patients showed an increased coagulability and these patients were resistant to dicumarol These findings indicate that the Waugh Ruddick test is not abnormal in a significant percentage of patients suffering acute coronary occlusion

The prothrombin time was determined by the method of Quick using thromboplastin prepared from rabbit brain Normal values were taken as 15 to 22 seconds for whole plasma and 60 to 80 seconds for 12 5 per cent diluted plasma values which do not conform with those which Dr Quick demands from his technic

The results fail to reveal any constant shortening of the prothrombin time in instances of acute coronary occlusion at the time of hospital admission or during the course of the illness The authors found no evidence that hypo or hyperprothrombinemia is a constant accompaniment of acute coronary thrombosis

The clotting time of the whole blood was determined by the three tube method of Lee and White and times of from 10 to 15 minutes were considered to be normal Only two patients had a value of less than 10 minutes upon admission No constant variation in clotting time was noted during hospitalization on the 13 patients not receiving anticoagulant The patients receiving dicumarol tended to show a slightly prolonged coagulation time

The authors concluded that no constant changes in blood coagulability could be demonstrated following an acute coronary occlusion by the Waugh Ruddick test the prothrombin time or

three types (I) no fibrinogen B is found (II) fibrogen B absent transiently and then present again or (III) fibrinogen B present constantly Irrespective of these findings heparin and dicumarol are given On the third day a fibrinogen B determination and a prothrombin time are done If the result of the fibrinogen B determination is negative no further anticoagulant is given If fibrinogen B is present anticoagulant therapy is continued

Voorhees and Pulaski (650) performed 553 tests for fibrinogen B and 337 determinations of the capillary clotting time on 48 hospital patients and on four normal subjects In only two instances were the criteria of Cumminge and Lyons for inevitable thrombosis fulfilled but neither patient developed clinical evidence of intravascular thrombosis On the basis of their experience Voorhees and Pulaski concluded that the test is of no particular value in confirming a diagnosis of thrombophlebitis They did notice however an apparent relation between the presence of tissue necrosis and the appearance of fibrinogen B in the circulating plasma and a persistently negative test for fibrinogen B in thrombophlebitis after it is initially positive both observations having previously been made by Cumminge and Lyons

Dunn Jackson and Lyons (651) have recently reported a high percentage of positive fibrinogen B tests in the following conditions 97 per cent of patients in congestive heart failure 100 per cent of patients with recent coronary occlusion 100 per cent of patients with thrombotic states 100 per cent of patients with acute sepsis and 90 per cent of patients with chronic sepsis John Beyer working in our laboratory has failed to confirm the work of Lyons et al Even patients with early or advanced thrombotic states usually failed to show positive tests for fibrinogen B

Changes in Coagulability in Coronary Occlusion with Myocardial Infarction

Hilton et al (652) studied the changes in the Waugh Ruddick test the prothrombin time coagulation time blood volume circulation time hematocrit and plasma proteins on a series of 31 cases of acute coronary occlusion Alternate patients received anticoagulant therapy Blood studies were performed at the time of admission and weekly thereafter except that the prothrombin

CHAPTER 31

The Effect of Certain Drugs on Coagulation and on the Prothrombin Time

The Xanthines

BLOOD and Patterson (654) reported that they were unable to confirm previous observations that aminophyllin possesses a thromboplastic action with an accelerating effect on blood clotting which might predispose to intravascular thrombosis Following the administration of aminophyllin orally and by vein no statistically significant changes were detectable in the clotting time or in the prothrombin activity of hospital patients with normal hepatic function and hematological findings

McCormick and Young (655) administered large single doses of aminophyllin (25 to 100 mg per kg body weight) intravenously to dogs and determined the prothrombin activity by the modified two-stage method of Seegers There was a transient elevation in prothrombin activity followed by a late hypoprothrombinemia and a return to normal in about two to three weeks Simultaneously a more marked and more persistent rise in Ac globulin activity occurred as determined by the method of Ware and Seegers Small doses of aminophyllin (6 mg per kg body weight) were without significant effect

No correlation could be ascertained between the clotting time of whole blood (Lee White method) and variations in the prothrombin and Ac globulin activity

Digitalis and the Digitaloids

Honorato and Lopetegui (656) studied the influence of a single dose of Digilanid Digitalin ouabaine cholic acid and Cumarone on the prothrombin time of rabbits All of these drugs shortened the prothrombin time The authors caution that special care must be taken to work with diluted plasmas because the normal con

the coagulation time of the whole blood A high percentage of patients had prolonged circulation times due to shock heart fail ure or a combination of these factors

Meyers (653) who had previously reported that the prothrombin time becomes shortened in cases of myocardial infarction studied 28 patients with acute myocardial infarction to determine whether changes occur in the plasma fibrinogen in such instances Plasma fibrinogen was determined on each patient two or three times a week by digestion and nesslerization of the fibrin clot A normal control studied for four months had fibrinogen values of 0 2 and 0 3 grams

In all instances of definite myocardial infarction there was an increased value for plasma fibrinogen which paralleled the ery throcyte sedimentation rate rather closely The amount of plasma fibrinogen paralleled the extent of the infarct When the presence of an infarct was equivocal and the erythrocyte sedimentation rate was normal fibrinogen levels were not abnormal Elevated fibrino gen levels failed to return to normal though they were always moving in that direction at the time of the patient s discharge In two patients given dicumarol fibrinogen levels were elevated despite the prolonged prothrombin time The author suggests the use of plasma fibrinogen levels for determining the status of an infarct in the presence of anticoagulant therapy

Three other patients whose prothrombin activity was kept between 10 and 30 per cent of normal by the administration of the necessary doses of dicumarol were given digitalizing doses of digitoxin There was no rise of prothrombin activity above the aforementioned levels following digitoxin

These data do not support the view that digitalis promotes coagulation of the blood

Cathcart and Blood (659) undertook to determine if digitalis modifies the clotting time and the prothrombin time in vivo They quote the following papers in the literature

(1) Tanaka (438) who first stated that strophanthin shortened the clotting time of blood

(2) Werch (440) who described a decrease in the clotting time of rabbits following digitalization

(3) Decourt and Barbato (660) who reported a decrease in the coagulation time in 32 digitalized patients

(4) Massie Stillerman Wright and Minnich (83) who found a decrease of the clotting time in digitalized patients which averaged 3 3 minutes

(5) Ramsey Pinschmidt and Haag (85) and Sokoloff and Ferrer (84) who found no change in the clotting time following digitalis

(6) Macht (81) who reported that heparinized cats are less susceptible to toxic doses of digitalis than were untreated animals

(7) de Takats (82) who found that digitalized animals were unusually insensitive to heparin administration (heparin tolerance test)

(8) Moses (412) who using a similar test found no change in the clotting time or in the response to heparin following intravenous digitalis and

(9) Poindexter and Meyers (418) who found no change in the prothrombin time following adequate digitalization

Cathcart and Blood studied two groups of patients before and after digitalization 17 patients in congestive heart failure and 21 *normal hospital personnel* Fourteen hospital patients were used as controls In the control group the diseases which led to hospitalization varied but in no instance was there any disorder of the liver or of the blood forming organs nor any medication which might be expected to interfere with blood clotting Coagulation times were determined by two methods (Lee White and Leifer)

centration of the factor apparently responsible for this result is very high

An increase of a plasma protein resembling the co factor of thromboplastin was found and is suggested as an important factor in the shortening of the prothrombin time Increases of fibrinogen thromboplastinogen and prothrombin were not responsible for the results obtained

The authors also claim to have confirmed an antagonism between the effects of digitalis and dicumarol *Honorato* and Gomez (657) found that 0 1 mg per kg body weight of dicumarol is sufficient to prevent the shortening of the prothrombin time produced by 01 *mg per kg body weight of Digilanid No decrease in cardio* tonic potency was observed in tests conducted on the frog even when 0 5 mg of dicumarol was used

Experimental thrombosis was readily produced in rabbits treated with Digilanid but was prevented by the administration of dicumarol The differences in results between the treated and con*trol groups were significant*

Clinical Reports

Levin and Ruskin (658) performed heparin tolerance studies on 11 patients who had no evidence of cardiac decompensation or thromboembolic disease The tests were done before and after the patients had received a full digitalizing dose (1 6 mg) of digitoxin The tolerance tests were done as described by de Takats and by a modified method using the Lee and White coagulation time technic The heparin tolerance curves displayed no significant changes following digitoxin when the capillary tube technic was used Seven of the same 11 patients showed no significant changes in heparin tolerance after digitoxin when the Lee and White method was used Two showed decreased tolerance to heparin after digitoxin using this same technic

The problem was studied further by performing prothrombin times on nine similar patients before and after administration of digitoxin There was no significant change in the prothrombin time These subjects were then given dicumarol in doses of 300 mg 200 mg and 100 mg on 3 successive days while on a maintenance dose of digtoxin (0 2 mg /day) In all instances the response to dicumarol was considered normal

Some patients showed slight shortening others slight prolongation of the clotting time These changes were not always in the same direction by the two methods There was no significant difference in the response of the clotting time to digitalis whether or not the patients were in congestive heart failure Changes in the patients receiving digitalis were of no greater magnitude than in the normal

The prothrombin times of the whole plasma in the normal controls and in the undigitalized hospital patients averaged 13 34 seconds (range from 11 9 to 17 8 seconds) All but one determination on one subject fell within a range of 13 5 seconds ± 1 6 seconds With 12 5 per cent plasma the average prothrombin time was 31 0 seconds (over all range 25 5 to 42 5 seconds) The range was quite wide and the end point less reliable

In the patients with congestive heart failure the average prothrombin times for whole (undiluted) plasma were 14 6 seconds before and 13 8 seconds after digitalization a decrease of 0 8 seconds or 5 per cent Using 12 5 per cent plasma the average prothrombin times before and after digitalization were 32 3 seconds and 30 0 seconds respectively a decrease of 2 3 seconds or 7 per cent

In normal subjects who were digitalized the initial prothrombin time with undiluted plasma was 13 1 seconds and the final time 13 5 seconds a change of 0 4 seconds or 3 per cent

In the controls the initial time with undiluted plasma was 13 6 seconds and the final time 13 4 seconds a decrease of 0 2 second or 2 per cent With dilute plasma the average times were 28 9 seconds and 30 7 seconds an average increase of 1 8 seconds or 6 per cent

As with the coagulation times there was no constant trend toward either a prolongation or a shortening of the prothrombin time The average time at the start of the study was comparable in all groups and the daily average changes following digitalization were insignificant

The authors conclude that there are no statistically significant changes in either the clotting or prothrombin times following the administration of digitalis in therapeutic doses

before and every day for five days after digitalization Prothrombin times were determined on both undiluted and 12 5 per cent diluted *plasma*

Of the patients in congestive failure 14 were digitalized with an average dose of 2 1 mgm (1 5 2 4) of digitoxin in five days Two were digitalized with Lanatoside C by intravenous injection and then 1 2 mg of digitoxin were given by mouth during the subsequent four days The third *patient received* 1 2 mgm of Lanatoside C intravenously and a total of 5 Units (U S P XII) of digitalis leaf by mouth during the next five days The desired therapeutic response was obtained clinically in all patients

Normal subjects who were digitalized were treated as follows four received 18 20 U S P Units of digitalis leaf in five days 17 received 1 8 3 0 mg (average dose 2 mgm) of digitoxin in five days Two patients experienced minor toxic symptoms

The clotting time of normal controls including the undigitalized hospital patients and the hospital personnel before digitalization averaged 11 6 minutes by the Lee White method (range from 8½ to 19 minutes) 6 2 minutes by the Leifer method (range of four to 10 minutes) In patients with congestive heart failure before digitalization the average coagulation time was 11 9 minutes by the Lee White method Following digitalization the average time was 11 1 minutes an average decrease of 0 8 minute or 7 per cent By the Leifer method the clotting times before and after digitalization averaged 6 1 and six minutes respectively an average change of only 0 1 minute or 2 per cent In the normals who were digitalized the coagulation time by the Lee White method averaged 12 1 minutes before and 12 3 after digitalization *an average change of 0 2 minute or 2 per cent* By the Leifer method there was no change with digitalization 6 6 minutes being obtained both before and after

In the control patients who received no digitalis the average clotting time was 10 7 minutes at the beginning and 11 minutes at the end of the study by the Lee White method a change of only 0 3 minute or 3 per cent With the Leifer method the corresponding times were 5 6 and 6 3 minutes a change of 0 7 minute or 13 per cent

that these hemorrhages may be attributed to a lowering of the pro thrombin activity by the penicillin

Streptomycin

To determine the effect of *oral* streptomycin on the prothrom bin time Hertfort and Standard (633) administered 3 grams of the antibiotic daily to four normal subjects for 14 days The pro thrombin times and the bacterial count of the stool were deter mined for each subject on two different days prior to the institu tion of oral streptomycin 24 hours after the administration of the antibiotic and at 48 to 72 hour intervals throughout the 14 day period There was no attempt to modify the diet

There was a diminution in stool bacterial counts varying from an 80 to 100 per cent reduction demonstrating that the antibiotic varies in its effectiveness in different individuals In all subjects the maximum reduction in bacterial count was achieved within 48 hours after the administration of streptomycin Concomitant with the decreased bacterial counts in the stool there was a signifi cant prolongation in the prothrombin times of whole blood and 12 5 per cent diluted plasma as determined by the Link Shapiro modification Whole blood prothrombin times rose from 16 to 19 seconds to maximums of 22 to 24 seconds The peak of the hypo prothrombinemia was reached within one to four days With dilute plasmas the prothrombin times were prolonged from a pretreat ment level of 36 to 51 seconds to a maximum of 51 to 75 seconds These maximums were reached within from one to seven days

In all subjects the bacterial counts of the stools began rising progressively seven days after streptomycin administration was started As the bacterial count increased the prothrombin times subsequently decreased so that by the end of a fortnight both dilute and whole blood prothrombin times approached the levels prior to streptomycin treatment

The authors suggest that a vitamin K preparation be given before and after surgery of large bowel to prevent the develop ment of hypoprothrombinemia In eight cases of proven or sus pected lesions in the colon streptomycin was given orally in half gram doses every four hours for two days immediately preopera tively and in conjunction with parenteral synthetic vitamin K

ANTIBIOTICS*

Penicillin

Lewitus (661) in a letter to the editors of the Archives of Internal Medicine refers to an article by himself and Aschireli in which it was shown that in 94 per cent of patients who received penicillin there was a definite decrease of the prothrombin activity of the blood This depression of prothrombin activity which often reached to between 50 and 60 per cent of normal lasted during the entire period of penicillin administration It could be corrected by injections of vitamin K and was terminated spontaneously following the interruption of penicillin therapy The authors considered this effect to be analogous to a similar effect by the sulfonamides

Lewitus states that the confusion over the effect of penicillin on the prothrombin activity arises from the fact that in the first hours after the beginning of penicillin therapy there is sometimes an increase in prothrombin activity which persists for several days The prothrombinopenic effect of penicillin may become evident only after three to four days He states further that when treating infective thrombotic processes with combined penicillin dicumarol therapy much less dicumarol is necessary than is usually prescribed in order to attain an adequate depression of prothrombin activity

The prothrombinopenic effect of penicillin was noted also by Axtrup (662) who reported three infants less than six months of age who were observed to show a fall in prothrombin activity during treatment with penicillin Two of these infants showed a hemorrhagic tendency in one case so severe as to contribute to a fatal outcome The literature contains reports of hemorrhage as a complication in penicillin treatment Such phenomena result mainly when the penicillin is applied intrathecally but similar symptoms have also been noted after subcutaneous or intramuscular injection though only when the doses were very large It is possible

* See also (1) Dolkart R E Halpern B Larkin M Dey F L & De Takats G The effect of penicillin upon the clotting activity of blood in normal human subjects *J Pharmacol & Exper Therap 96* 291 294 (July) 1949 (2) Long P H Antibiotics and blood coagulation *J A M A 142* 19 50 (Jan 7) 1950

clotting time was determined by the method of Lee and White before and periodically after the administration of the aureomycin

When doses of aureomycin from 15 to 100 mg were administered to four rabbits blood obtained by cardiac puncture showed a shortening of the coagulation from a pre administration time of ten to eleven minutes to three to nine minutes after one hour and to 1½ to seven minutes after 1½ to three hours A report of an experiment on a single cat revealed that after the administration of 200 mg aureomycin the coagulation time fell progressively from 10½ to 11½ minutes to four minutes the maximum shortening occurring after approximately one hour Aureomycin was administered in doses of 250 or 500 mg to 14 human subjects whose coagulation times prior to administration ranged from 8½ to 14½ minutes In every instance there was a shortening in the coagulation time when determined from one to 3½ hours after the administration The reduced times ranged from 3½ to nine minutes Without exception the clotting times were shortened by from 1¼ to seven minutes on an average 3½ minutes

The authors state that prothrombin times in both animals and man were unaltered by the administration of aureomycin

Where peritoneal contamination was anticipated additional streptomycin was given parenterally for two days preoperatively and for two days postoperatively The vitamin K was continued postoperatively for a week In all eight cases the prothrombin time was maintained at the levels which existed before the administration of streptomycin there were no hemorrhagic complications and recovery was uneventful

Elson (664) studied the coagulation time of the whole blood and the prothrombin time in 21 cases of pulmonary tuberculosis treated with streptomycin and in 21 matched cases not so treated The details of case matching blood studies and methods are given in the original article The results were treated statistically

The findings in normal subjects and in tuberculous revealed that the blood clotting time and the prothrombin time are unaffected in tuberculosis and that there is no correlation of these times with age activity or extent of the lesion in either the control or streptomycin group

When serial clotting time were performed significant differences between the mean clotting time of some of the test periods were observed but the results were inconclusive and could not be ascribed with certainty to the influence of streptomycin No significant differences could be demonstrated between the mean *clotting times of the streptomycin and control groups obtained on* different days

No significant effects by streptomycin upon the prothrombin time could be demonstrated either by serial prothrombin times performed up to 1 5 hours following the administration of streptomycin or by the prothrombin times obtained on different days

In brief this study indicates that streptomycin probably has no influence on either the clotting times or the prothrombin time clinically

Aureomycin

Macht and Farkas (665) pursuing further studies of the effects of the antibiotics on blood coagulation have reported studies on the influence of aureomycin Experiments were done on rabbits cats and on humans who had not received any previous medication In all instances the aureomycin was administered *orally* The

man striking changes occurred in blood coagulation Further more the addition of the disodium salt of d 1 alpha tocopherol phosphate in vitro prolonged the clotting time of recalcified plasma and also prolonged the clotting time of prothrombin free human plasma when added in concentrations on the order of those found in human plasma A similar antithrombic activity was demon strated in vivo by measuring the thrombin clotting time of plasma following the intraperitoneal injection of alpha tocopherol into rats The authors suggest the possibility that tocopherol partici pates normally in maintaining the equilibrium which prevents intravascular clotting

Kay and his coworkers (669 671) have studied the influence of alpha tocopherol phosphate on coagulation at some length They conclude that (1) alpha tocopherol phosphate a potent inhibitor of thrombin occurs in the accelerator globulin fraction of plasma and in Cohn s fraction I (2) when antithrombin in this form is combined with fibrinogen and thrombin in optimum quantities a substance is formed which is indistinguishable from fibrinogen B (3) thrombosis is likely to occur when the plasma antithrombin level is abnormally low while the prothrombin conversion rate is at or near normal and (4) limited studies suggest that the anti thrombin level can be raised by the oral administration of alpha tocopherol and that the routine administration of alpha tocopherol in the postoperative period may prove to eliminate intravascular clotting as a postoperative complication

Popper et al (672) determined plasma tocopherol levels in vari ous normal and abnormal conditions both before and after the administration of a test dose of tocopherol The range of plasma tocopherol levels was significantly widened in a variety of diseases The plasma tocopherol level was increased in nephritis in the presence of carcinoma in obstructive jaundice and most con sistently in the presence of cardiac disease The plasma tocopherol levels were reduced slightly and not consistently in hepatocellular damage

Coagulation Defects in Leukemia and Polycythemia

The heparin clotting time which measures the clotting sensi tivity of the blood to added heparin and the clot retraction rate

CHAPTER 32

Miscellaneous Observations

Circulating Anticoagulants

CONLEY Hartmann & Morse (666) have described a test for circulating anticoagulants utilizing the effect of platelet free plasma on normal blood The preparation of the platelet free plasma depends on scrupulous technic siliconed syringes test tubes and pipets handling the blood at low temperatures and two separations by centrifugation at 7000 and 12 000 14 000 r p m By this method amounts of added heparin as low as 0 001 mg /ml of platelet free plasma were detectable In clinical studies eight instances of a circulating anticoagulant were detected In only one did the addition of toluidine blue suggest the presence of a heparin like substance In nine cases of thrombocytopenia the anticoagulant assays were negative These studies suggest that circulating anticoagulants are probably present more commonly than hitherto supposed The suggested technic offers another approach to the study of hemorrhagic diatheses

Conley Rathbun Morse and Robinson (667) reported three cases in which a hemorrhagic diathesis with prolonged clotting time was associated with the presence of an anticoagulant in the blood In one instance the anticoagulant in the patient s plasma delayed the conversion of prothrombin to thrombin but in two instances the anticoagulant appeared to interfere with the activation of thromboplastin in the blood These findings suggest a *multiplicity of circulating anticoagulants* The authors advise that the blood of all patients who suffer a prolonged clotting time should be assayed for the presence of circulating anticoagulants

*The Antithrombic Activity of Alpha Tocopherol Phosphate**

Zierler Grob and Lilienthal (668) observed that when alpha tocopherol phosphate was administered in large doses to rats or to

* See also Lemley J M Gale R G Furman R H Cherrington M E Darby W J & Meneely G R Plasma tocopherol levels in cardiac patients *Am Heart J* 37 1029 1034 (June) 1949

quently a prolonged blood clotting time Many of these patients also have a severe thrombopenia In other patients hemorrhages occur when the platelet count is normal Bleeding in the majority of these patients ceased upon the administration of adequate amounts of toluidine blue or protamine sulfate but the hemorrhagic diathesis produced by thrombopenia did not respond to this type of therapy In patients with idiopathic thrombopenia and with increased protamine titrations the response to toluidine blue and to protamine was inadequate Thrombopenia occurred with or without an increase in the protamine titration and vice versa The authors conclude that the random use of toluidine blue and of protamine sulfate will lead to random results

Allen and his coworkers (667) have described the protamine titration test which they utilize as an indication of the clotting defect in certain hemorrhagic states This test is described in Appendix E

Tanturi and Wetzel (675) present a hypothesis which suggests that heparin is the normal anticoagulant of plasma Their conclusions may be summarized as follows

1 Lyophilized aereated and aged plasmas show an increase of antithrombin activity as compared with the corresponding fresh plasma The antithrombin activity was studied using a thrombin solution of constant activity

2 The increased antithrombin activity is not related to the presence of prothrombin because the same changes occur in lyophilized aged and aereated prothrombin free plasmas

3 The effect of the increased antithrombin activity is reflected in the prothrombin times of these plasmas and on the prothrombin times of fresh plasmas when plasmas with increased antithrombin activity are used as diluents

4 The increased antithrombin activity may be brought back to normal by means of various treatments (CO_2 protamine)

5 The antithrombin activity varies directly as the pH of plasma However protamine sulfate decreases the antithrombin activity without changing the pH of the plasma It may be concluded that the decrease of prothrombin noted by other investigators in similar plasmas is due to the presence of the antithrombin and not solely due to changes of the pH

6 Protamine sulfate has a tendency to decrease prothombin

which is a quantitative measure of clot retraction obtained by electric resistance measurements were well standardized on a large number of normal subjects and limits of normal clearly established by Rosenthal (673) In both myelocytic and lymphocytic chronic leukemia half of the patients exhibited a coagulation defect characterized by (1) prolonged heparin clotting time (2) decreased clot retraction rate and (3) slight thrombocytopenia (110 000 to 180 000) The severity of the defect was closely related to the severity of the hemorrhagic symptoms Toluidine blue titration tests failed to demonstrate free or neutralizable heparin in two patients with hemorrhagic symptoms and the clotting defect Leukemic patients without the clotting defect presented no evidence of bleeding and these patients were in better condition hematologically and clinically and demonstrated a better prognosis than did the others

Untreated patients with polycythemia vera and elevated hematocrits showed increased clot retraction rates and platelet counts above 400 000 in one third of instances A similar percentage of these patients had histories of either thrombosis or hemorrhage suggesting that the elevation in platelet count is a most important factor in the occurrence of both thrombosis and hemorrhage in polycythemia

This study indicates the relative value of various coagulation tests The Lee White clotting time is of extremely limited value The platelet count bleeding time tourniquet test and clot retraction have limitations and inadequacies The clot retraction rate provides a useful quantitative measure of clot retraction but requires special equipment The heparin clotting time appears to be the most valuable single test for blood coagulation since it readily detects abnormally increased or decreased clotting ability either experimentally or clinically

HEPARINEMIA OR HYPERHEPARINEMIA

According to Allen and his coworkers (630) abnormal bleeding may result from a heparinoid disturbance in the clotting mechanism a state resembling but not identical with that produced by the intravenous injection of commercial beef heparin Patients with this defect show an increase in protamine titration and fre

similarity between acute total body irradiation illness and the radiation illness that follows localized therapy except that both are caused by ionizing radiation Administration of rutin to a small group of dogs for two weeks prior to exposure and continued use after exposure apparently improved their survival rate (682) Experiments showed rutin to be of no value in the treatment of three separate large groups of mice regardless of when rutin administration was started (683)

Following the identification of an anticoagulant with heparin like properties in acute radiation illness by Allen et al (487 498) and the confirmation of this work (497) it was hoped that control of the coagulation defect by antiheparin agents such as toluidine blue and protamine sulfate would decrease the mortality This has not yet been demonstrated

The Effect of Anticoagulants on the Erythrocyte Sedimentation Rate

Litwins Vesell Kissin Cohen and Paul (684) studied the effect of dicumarol on the sedimentation rate in (1) persons with normal sedimentation rates (2) patients with myocardial infarction and elevated sedimentation rates who received dicumarol therapeutically and (3) other patients with elevated sedimentation rates who did not require anticoagulant therapy The sedimentation rate was determined in Wintrobe tubes by a single reading at 60 minutes Prothrombin times were determined by the method of Quick

Among the 12 patients with normal sedimentation rates given dicumarol in amounts sufficient to reduce the prothrombin activity to as low as 3 per cent of normal the sedimentation rates remained normal

Among seven patients with acute myocardial infarction given dicumarol in amounts sufficient to maintain the prothrombin activity between 5 and 20 per cent of normal dicumarol did not increase the sedimentation rate which diminished gradually during the early stages of the illness despite the progressive prolongation of the prothrombin time Seven additional cases of myocardial infarction treated with dicumarol showed no discrepancy between the recorded sedimentation rate and the state of healing clinically

Among eight patients with medical conditions other than myo-

and precipitate fibrinogen depending upon the quantity present

7 With appropriate quantities of protamine sulfate the antithrombin activity of fresh oxalated normal plasma can be reduced to a certain extent but no more irrespective of the amount of protamine used An approximate proportion between the quantity of protamine necessary to return to normal the thrombin times of certain plasmas and to reduce the antithrombin activity of normal plasmas has been demonstrated

The Effect of Ionizing Radiation Upon the Blood

Cronkite and Chapman (676) have made a critical analysis of the syndrome of acute total body radiation illness They describe in brief what is known of the pathogenesis of the hemorrhagic diathesis that is so prominent in acute radiation illness particularly in the lethal dose range

In the early phase capillary fragility is increased later a platelet deficiency develops As the thrombopenia progresses purpura becomes more evident In the last days hemorrhage may become profuse at which stage the blood clotting time and occasionally the one stage prothrombin time is prolonged Generally heparin can be titrated by indirect means in dogs (187 498) and in swine and goats (197 677 678)

In addition to the routine clinical observations and physical examinations the following studies are definitely indicated for purposes of therapeutic control and clinical investigation

(1) Platelet counts should be performed every two to three days A return of platelets will usually precede the cessation or lessening of bleeding and in general is a good prognostic sign

(2) Capillary fragility should be studied and it would be of great interest to do this in conjunction with the administration of rutin

(3) Whole blood clotting times (Lee White) prothrombin times (Quick) fibrinolysin titers (679) and heparin and heparin complement assays (680 681) and tolerances should be performed in order to establish the presence of and to clarify the nature of the clotting defect in man

Most of the drugs that have been suggested were advised on the basis of their value in the treatment of radiation sickness that follows localized therapeutic irradiation There is no great

SECTION XI

APPENDICES

cardial infarction and rapid sedimentation rates given dicumarol in amounts sufficient to produce therapeutic prolongations of the prothrombin time the sedimentation rate paralleled the observed clinical course

These findings confirmed the original work of Prandoni and Wright previously discussed in this volume

APPENDIX A

Method of Determining the Coagulation Time of Whole Blood

(One Tube Method of Lee and White)

ONE ml of blood is withdrawn from the arm vein using a small all glass syringe The time at which the blood is drawn is noted The needle is removed and the syringe then emptied into a small glass tube (Widal tube) about 8 mm in diameter which has previously been rinsed out with physiologic saline solution (85 per cent) The tube is rotated endwise (tilted) every 30 seconds and that point at which the blood no longer flows from its position but maintains its surface contour when inverted is taken as the endpoint Care must be used to exclude air bubbles as they tend to accelerate coagulation If the test is done at room temperature (65° 90° F) the error although present is within one minute and may be neglected Normal coagulation time is 6½ minutes (5 8 minutes)

REFERENCES

Lee R L and White I D A clinical study of the coagulation time of blood *Am J M Sc* 145 495 503 April 1913

not ground under a layer of acetone The spent acetone is poured off the brain covered with fresh acetone and the trituration repeated This is continued until the preparation becomes adhesive and flaky It is then ground under fresh acetone until granular The material is filtered by suction and dried at 37° C for 30 minutes

By placing the material in glass ampoules evacuating by means of an oil vacuum pump and sealing in a glass flame full potency can be preserved indefinitely An alternative method of preservation is to place 0 2 gm of the dry material in small pyrex test tubes cover with 5 cc saline solution (0 85 per cent) and place immediately in the freezing compartment of a refrigerator The material remains fully potent for at least 2 weeks It requires incubation at 50° C before it is ready for use

III The Test

Nine volumes of blood obtained by venipuncture are mixed with 1 volume of 0 1 M sodium oxalate If it is difficult to obtain blood by a vein a deep skin cut should be made and the blood allowed to drop into test tube or conical centrifuge tube having a 1 cc graduation and containing 0 1 cc of 0 1 M sodium oxalate The 1 cc sample thus obtained is sufficient for 4 prothrombin determinations It is convenient to remove plasma by means of a pipette having a rubber bulb from a medicine dropper attached to the end

The prothrombin time is determined by transferring 0 1 cc of oxalated plasma to a small pyrex test tube and then adding 0 1 cc of thromboplastin solution After the tube has been in the water bath for a few seconds 0 1 cc of 0 02 M calcium chloride is blown forcibly into the mixture and the stop watched clicked simultaneously The tube is put in the water bath and shaken lightly

A few seconds before the expected clotting time the tube is held toward a distant source of light so that one can see through the tube from below The tube is tilted very gently to permit detecting the incipient web of fibrin which is the end point If the tube is shaken too vigorously the initial fibrin mesh is apt to be broken and so escape detection More time will therefore be

APPENDIX B

The Determination of Prothrombin

(By the Method of Quick)

I Required Equipment

1 Pipettes—1 cc serological graduated in tenths and hundredths of a cc The pipettes should be cut to 170 mm lengths

2 Water bath A glass dish 8 to 10 inches in diameter and 4 to 5 inches deep will serve the purpose It should be on a base containing two 25 watt electric light bulbs These supply sufficient heat to maintain the temperature fairly well at 37°C

3 A thermos bottle filled with water at 50° C for incubating the thromboplastin solution

4 A stop watch

5 Test tubes pyrex (13 × 100 mm)

II Reagents

1 Sodium oxalate 0 1 M—1 34 gm sodium oxalate C P is dissolved in 100 cc of distilled water

2 *Calcium chloride 0 02 M*—0 222 gm anhydrous *calcium* chloride is dissolved in 100 cc of distilled water

3 Thromboplastin solution—0 2 gm of dehydrated rabbit brain is put into a small pyrex test tube covered with 5 cc of 0 85 per cent sodium chloride solution and mixed by blowing through the suspension with a pipette Triturating the thromboplastin with saline in a mortar should be avoided since this reduces the activity After incubating the solution for 20 minutes at 50° C it is tranferred to the water bath kept at 37° C Agitation of the solution by blowing through it helps to maintain a uniform activity Suspended particles do not interfere with the accuracy of the test but actually aid in the detection of the incipient clot

4 *Preparation of thromboplastin* The rabbit brain is freed of all visible blood vessels and then triturated with acetone in a glass mortar The material at first should be mashed and crushed but

not ground under a layer of acetone The spent acetone is poured off the brain covered with fresh acetone and the trituration repeated This is continued until the preparation becomes adhesive and flaky It is then ground under fresh acetone until granular The material is filtered by suction and dried at 37° C for 30 minutes

By placing the material in glass ampoules evacuating by means of an oil vacuum pump and sealing in a glass flame full potency can be preserved indefinitely An alternative method of preservation is to place 0 2 gm of the dry material in small pyrex test tubes cover with 5 cc saline solution (0 85 per cent) and place immediately in the freezing compartment of a refrigerator The material remains fully potent for at least 2 weeks It requires incubation at 50° C before it is ready for use

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required before sufficient fibrin will again be formed to become visible and this introduces an appreciable error.

When the prothrombin time is greatly prolonged it is convenient to use a large test tube (25 × 100 mm.) filled with water at 37.5° C. as a jacket. The large tube is fitted with a cork with a hole through which the smaller test tube can be inserted and held in place. This device allows continuous observation while the temperature of the reacting medium is maintained constant.

Calculation. Due to the complex nature of the prothrombin it is best to express results in terms of prothrombin activity. When the prothrombin activity (in per cent of normal) is plotted against the clotting time a characteristic hyperbolic curve is obtained which is fairly satisfactorily expressed by the equation

$$\text{Prothrombin activity (per cent of normal)} = \frac{k}{p.t. - a}$$

(p.t. = prothrombin time. k and a are constants with the value of 303 and 8.7 respectively)

For convenience the following table can be used.

Prothrombin Time	Prothrombin Activity in Per Cent of Normal
11 12½	100
13½	60
15	50
17	40
19½	30
21½ 22	25
24 26	20
37 40	10
55 65	5

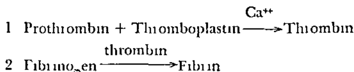
It is to be noted that neither the equation nor the table is valid unless a thromboplastin of constant potency is used. The prothrombin time obtained on a normal control plasma must fall within the limits of 11 to 13 seconds. It is to be emphasized that it is completely erroneous to calculate prothrombin activity by dividing the prothrombin time of the normal by that of the unknown.

APPENDIX C

Two-Stage Prothrombin Determination[1]

THEORETICAL

PROTHROMBIN clots fibrinogen only after it has been activated to thrombin *The equations are often written as follows*



$$1 \quad \text{Prothrombin} + \text{Thromboplastin} \xrightarrow{Ca^{++}} \text{Thrombin}$$

$$2 \quad \text{Fibrinogen} \xrightarrow{\text{thrombin}} \text{Fibrin}$$

In the one stage methods for prothrombin analysis reactions one and two are allowed to occur simultaneously In the two stage method reaction one is allowed to go to completion Thereafter the second reaction is used to measure thrombin concentration The fundamental relationship between thrombin concentration and clotting time is described in detail elsewhere (1) A unit of thrombin is arbitrarily defined as the amount which will clot *one cc of fibrinogen under the conditions imposed for the two* stage analysis This unit is for all practical purposes the same as the one used by government agencies for controlling and standardizing thrombin products sold on the market

It can be noted from the equations above that the measurement of thrombin concentration by means of reaction two requires the use of fibrinogen Rather than assume that the patient s fibrin

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[1] This description is that contributed by Walter H Seegers to the *Transactions of the First Conference on Blood Clotting and Allied Problems* New York Josiah Macy Jr Foundation 1948 It gives the procedure used in the Department of Physiology Wayne University as of January 1948 The original communications of Warner Brinkhous and Smith are in *Arch Path* 20 163 (1935) *Am J Physiol* 114 667 (1936) *J Exper Med* 66 801 (1937) Our modifications have no bearing on theoretical matters but are modifications *of convenience gained through experience* An exception is however to be found in the innovation which supplies Ac globulin In practice that change is so simple that one should scarcely be credited with having made a modification —Walter H Seegers

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55 65	5

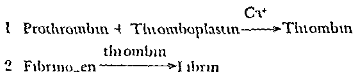
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ogen is normal in quantity and quality it is supplied as a standard ized reagent prepared in the laboratory

Factors concerned with prothrombin activation are kept under control These are pH salt concentration thromboplastin cal cium ion concentration and colloid concentration even anti thrombin is largely eliminated In the new modification Ac globu lin is controlled Since there is as yet little information concerning variations in Ac globulin concentration in health and disease no one is able to estimate to what extent this factor may have been an influence in the two stage method reports When applied to the analysis of purified prothrombin it is an important consideration

Practical Remarks

There is considerable latitude in the practical use of this method Only a few items need to be mentioned by way of illus tration (a) Any suitable anticoagulant such as oxalate or citrate may be used (b) One cc of blood can be sufficient (c) Storage of the plasma for a day or so in the deep freeze does not alter the results significantly (d) Changes in the patient s fibrinogen con centration or its quality do not influence the results (e) The reagents can be used for the quantitative determination of puri fied prothrombin (f) The reagents can be used for the measure ment of thrombin concentration (g) The results can be expressed in per cent of normal or in absolute units (h) A good technician can make 20 determinations in 1 day (i) The method can be adapted to the quantitative determination of Ac globulin con centration (j) The reagents employed can be used for the study of antithrombin activity

Determination of Prothrombin

For the actual determination of prothrombin the blood is drawn by ordinary venipuncture into a clean syringe The manipulation should be completed with reasonable promptness so that no pro thrombin becomes activated to thrombin The blood is then delivered into a suitable quantity of anticoagulant The volume of anticoagulant must however be noted For example 7 parts of blood may be delivered into a graduated centrifuge tube

containing 1 part of 1 85 per cent $K_2C_2O_4$ Proper mixing must be insured and the specimen in a beaker with ice may be taken to the laboratory in due course of time and centrifuged in a graduated tube so that the hematocrit can be recorded Although it is not absolutely necessary to centrifuge in the cold it is unadvisable to centrifuge for prolonged periods of time on hot summer days The plasma can be analyzed immediately or after 24 hours storage in a deep freeze at $-20°$ C or colder

Three basic reagents are required for the determination

(1) Standardized thrombin solution is needed for defibrination

(2) Incubation mixture is used for activating prothrombin to thrombin It contains thromboplastin in excess calcium ion in correct concentration imidazole buffer and colloidal acacia

(3) Fibrinogen is needed to measure thrombin concentration

Specific Procedure

1 The blood is centrifuged The hematocrit is determined and the plasma drawn off

2 0 5 cc plasma is mixed with 0 5 cc saline and 0 1 cc of thrombin (100 Iowa units per cc) solution is added This is allowed to stand 10 minutes and the clot is wrapped on a stirring rod The antithrombin destroys the added thrombin

3 Saline dilutions are made according to the following examples

1 20 = 0 1 cc defibrinated plasma + 0 9 cc saline
1 30 = 0 1 cc defibrinated plasma + 1 4 cc saline
1 40 = 0 1 cc defibrinated plasma + 1 9 cc saline
1 50 = 0 1 cc defibrinated plasma + 2 4 cc saline

4 Fibrinogen (0 1 cc) is placed into a series of 6 test tubes (10 × 75 mm)

5 Take 1 0 cc diluted defibrinated plasma and add it to 3 0 cc of reaction mixture Allow activation of prothrombin to proceed and at 1 minute intervals add 0 4 cc of the mixture to a fibrinogen tube Note clotting time in seconds The tube is tilted repeatedly to the horizontal position and viewed from below toward

a suitable source of light The first definite visible signs of fibrin are taken as the end point Shortly after the end point is reached a rather more solid clot forms

Select the dilution giving a clot nearest to 15 seconds Maximum activation of prothrombin can usually be expected in 3 minutes with dog and bovine plasma and in 5 minutes with human plasma A *15 second clot represents unit concentration and in the computation* it must be remembered that the diluted prothrombin (Step 3 above) again becomes diluted 5 fold in the final clotting mixture The units of prothrombin in the plasma without correction for anticoagulant can be noted from the following table

UNITS OF PROTHROMBIN IN PLASMA
VARIOUS CLOTTING TIME AND VARIOUS DILUTIONS ARE GIVEN

Saline	Observed clotting time in seconds							
Dilution	13 0	13 5	14 0	14 5	15 0	15 5	16 0	16 5
Factor	Units prothrombin per cc oxalated plasma							
1 60	396	379	360	343	330	317	301	293
1 55	363	348	330	314	302	290	278	269
1 50	330	316	306	286	275	264	253	245
1 45	297	284	270	257	248	238	228	220
1 40	264	253	240	229	220	211	202	196
1 35	231	221	210	200	193	185	177	171
1 30	198	190	180	171	165	158	152	147
1 25	165	158	150	143	138	132	127	122
1 20	132	126	120	114	110	106	101	98
1 15	99	95	90	86	83	79	76	73
1 10	66	63	60	57	55	53	51	48
1 8	53	51	48	46	44	42	40	39
1 5	33	32	30	29	28	26	25	24
1 4	26	25	24	23	22	21	20	20
1 3	20	19	18	17	17	16	15	15
1 2	13	13	12	11	11	11	10	10
1 1	7	6	6	6	6	5	5	5

Example Total volume = 7 5 cc
Cell volume = 2 9 cc
Oxalate volume = 1 1 cc
7 5 − (2 9 + 1 1) = 3 5 plasma volume
7 5 − 2 9 = 4 6 volume titrated

Table for saline dilution factor vs observed clotting time

$$\frac{4.6}{3.5} \times \text{value from table} = \text{prothrombin in units}$$

$$\frac{\text{Patients prothrombin units}}{\text{Control prothrombin units}} \times 100 = \% \text{ of normal}$$

MODIFIED TWO STAGE

In item 3 above under specific procedure the defibrinated plasma is diluted with saline containing Ac globulin Go to the packing house and obtain beef blood After 2 hours centrifuge and obtain serum Take 1 cc serum plus 200 cc saline Use this saline for diluting the defibrinated plasma Store unused serum in deep freeze All else is exactly as described above for the regular two-stage procedure

LABORATORY EQUIPMENT

The laboratory arrangements can vary considerably to give convenient access to the following essential items

(1) Stop watch activated by a foot pedal
(2) 0 1 cc serological pipettes
(3) 0 2 cc serological pipettes
(4) 1 0 cc serological pipettes
(5) 5 0 cc serological pipettes
(6) Bin containing 10 × 75 mm serological test tubes without rim
(7) Bin containing 36 × 150 mm test tubes without rim
(8) Stock of 0 9% NaCl for dilutions
(9) Test tube rack
(10) Constant temperature bath set at 28° C for use if room temperatures deviate more than 2 or 3 degrees from 28

The glassware used for this work should always be clean It is well to have a container partly filled with water so that used glass ware can be kept moist Dried protein solution in glassware is an unnecessary nuisance These are then well rinsed in water and immersed in chromate H SO cleaning solution overnight We have found it helpful to adhere to the rigid rule that this chromate H_2SO_4 cleaning solution may not be used for any other purpose in the laboratory For cleaning the serological test tubes stainless

steel baskets are used (Central Scientific No 48525) For the larger tubes stainless steel beakers are passably satisfactory The next day the glassware is rinsed thoroughly in tap water in distilled water drained and dried in an ordinary oven

REAGENTS

Standardized Thrombin Solution The solution is prepared by dissolving the contents of one ampoule of Thrombin Topical (Parke Davis & Co) in 50 cc of glycerol The glycerol should be c p glycerol dissolved in physiological saline 50 50 Actually 75 per cent glycerol is a better stabilizing agent (2) but 50 per cent is preferred The thrombin can be stored in an icebox for a month or more In certain special circumstances it is well to bear in mind that the Thrombin Topical contains calcium thromboplastin carbohydrate and Ac globulin

Calcium Solution Dissolve 0 40 grams NaCl and 0 67 grams $CaCl_2$ in 100 cc water

Acacia Solution Dissolve 15 grams purified acacia in 0 9 per cent NaCl solution

Imidazole Buffer We synthesize much of our own imidazole Recently it has been possible to secure prompt delivery of good quality material from Edcan Laboratories 10 20 Pine Street South Norwalk Connecticut Dissolve 1 72 grams in 90 cc of 0 1 N HCl and dilute with water to 100 cc The pH should be 7 25

Crude Lung Extract Obtain a beef lung and wash thoroughly in cold water Cut into pieces and grind in a domestic meat chopper Set aside in the icebox 24 40 hours Strain and centrifuge Store in a deep freeze Before using dilute 1 8 with saline

Fibrinogen Several sources are suitable The preparation of Ware Guest and Seegers (3) is obtained as a 1 per cent solution (0 9 per cent NaCl + 10 per cent imidazole buffer by volume) It is well to distribute in serological tubes Store in deep freeze Thaw in water bath at 37°C with rotation of the tube

Purified Acacia Commercial acacia contains calcium which must be removed 400 g powdered acacia U S P are dissolved in 4 liters of water To this 40 grams of $K_2C_2O_4$ are added The solution is allowed to stand 5 days and then heated to 70°C The precipitate of calcium oxalate is removed with the aid of a lab

oratory model Sharples super centrifuge turbin drive at 50 000 R P M The clear solution is then dialyzed against demineralized water until free of oxalate The acacia is then precipitated by adding 3 volumes of alcohol and 200 grams of NaCl The latter breaks the stability of the colloidal solution This is allowed to stand over night The supernatant solution is discarded and the acacia is dried with alcohol dry alcohol and finally with ether A white powder is obtained Check the purified acacia to make sure that it is not contaminated with sodium chloride

Reaction Mixture
- 3 parts Crude Lung Extract 1 to 8
- 2 parts Calcium Solution
- 2 parts Acacia Solution
- 1 part Imidazole Buffer
- 1 part Saline

The reaction mixture can be stored at −20°C or colder for periods of time up to 2 months A quantity required for use can be thawed in a warm water bath and may be kept at room temperature for at least 6 hours Reaction mixture may also be dried from the frozen state and stored in sealed ampoules for several years For that reason the material can be prepared and standardized at a central laboratory and distributed for use in other laboratories The dry powder can be restored in solution by adding to it the requisite amount of water

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2 Seegers *Arch Biochem* 3 363 1944
3 Ware Guest and Seegers *Arch Biochem* 13 231 1947

APPENDIX D

Method for the Determination of Prothrombin Clotting Time

(Link and Shapiro Modification of Quick s Method)

METHOD

ALL quantitative methods based on empirical rather than *stoichiometric relationships can give reliable and reproducible* results only by strict conformity to rigidly standardized manipulative conditions This is especially true for the prothrombin time determinations since one is dealing here with the sensitive and variable process of blood coagulation If the procedure given below is followed carefully reproducible results will be obtained

Reagents and Solutions

1 Sodium oxalate reagent grade anhydrous Prepare in a volumetric flask a 0 1 M solution (13 4 grams dissolved in distilled water and made up to 1 000 ml)

2 Sodium chloride reagent grade Prepare in a volumetric flask an 0 85 per cent solution (8 5 grams dissolved in distilled water and made up to 1 000 ml)

3 Calcium chloride reagent grade anhydrous Prepare in a volumetric flask 0 025 M solution (2 77 grams dissolved in distilled water and made up to 1 000 ml)

4 Thromboplastin calcium chloride suspension To 5 0 ml of 0 85 per cent sodium chloride solution in a 15 ml centrifuge tube 0 1 grams of thromboplastin is added The mixture is agitated thoroughly The temperature of this suspension is maintained at 54 55 degrees C in a water bath for 10 minutes with constant agitation and then cooled to 25 26 degrees C To the suspension 5 ml of 0 025 M calcium chloride solution is added The mixture is stirred for 4 minutes and centrifuged 4 minutes at 1 700 R P M The centrifuge is brought to a standstill slowly so as to avoid resuspending the flocculent precipitate The slightly turbid super

natant solution is removed with a pipette and used in the deter mination

Procedure

To a test tube containing 0 5 ml of 0 1 M sodium oxalate solution 4 5 ml of freshly drawn blood are added This is quickly mixed The oxalated blood is centrifuged at 1 700 R P M for 10 minutes The clear plasma is then transferred with a pipette to a test tube The prothrombin time of the plasma should be de termined as soon as possible after collection

For the prothrombin time of whole plasma approximately 0 5 ml of plasma is transferred into a 75 × 10 mm test tube If diluted plasma is to be used 0 1 ml of plasma is transferred into another 75 × 10 mm test tube and diluted with 0 85 per cent sodium chloride To obtain a plasma concentration of 12 5 per cent 0 1 ml of plasma is diluted with 0 7 ml of saline The whole plasma and diluted plasma samples can be conveniently mixed by holding firmly the test tube near the top with the thumb and index finger and striking the lower end sharply with glancing blows using the index finger of the other hand This accomplishes a thorough mixing without contamination The whole and diluted plasmas are mixed thoroughly and placed in the constant tempera ture water bath at 37 degrees C

From the thromboplastin-calcium chloride suspension 0 2 ml is transferred into 100 × 12 mm test tubes with a 0 2 ml pipette (micro blood sugar) This suspension is blown into the test tubes and care is taken that the pipette is completely empty after each transfer These tubes are placed in the rack beside the whole and diluted plasma samples in the constant temperature bath

As soon as the contents of the tubes have reached the bath tem perature the prothrombin time of the plasma is determined as follows The tube containing the whole plasma is shaken again and 0 1 ml is transferred with a 0 1 ml pipette (micro blood sugar) to a tube containing 0 2 ml of the thromboplastin calcium chloride suspension The plasma is blown quickly from the pipette and at the same time the stop watch is started (The stop watch can be conveniently operated by a foot treadle) The tube is tapped sharply to mix the solutions This insures initiation of the clotting

process uniformly throughout the solution A small stirrer made of No 22 nichrome wire with a small loop on the end is then introduced If any small droplets are present on the sides of the tube they can be removed by passing the stirrer over them thus making certain that all of the constituents are in the bottom of the tube At this stage only 2 3 seconds should have elapsed since the time the plasma was added to the thromboplastin calcium chloride suspension

The mixture is stirred so that the stirrer loop sweeps across the test tube from 1 side to the other at a rate of 2 times per second *The end point (formation of clot) is that point at which the fibrin clot is sufficiently stable to be drawn to one side by the stirrer thus bringing into view a clear area* The clot is usually somewhat turbid since the calcium oxalate formed upon calcifying the oxalated plasma is enmeshed in the clot The formation of fibrids which impart a viscous appearance to the solution before the clot forms can be disregarded Record the number of seconds required for clot formation The same process is repeated using the diluted plasma

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APPENDIX E

The Protamine Titration[1]

1 Reagents and Equipment

(a) Protamine (salmine) sulfate stock solution 50 mg of powdered protamine sulfate (Lilly) are dissolved in distilled water and made up to 50 ml in a volumetric flask Do not use for 24 hours Keep refrigerated at 1 to 4° C (it is stable for one week)

(b) Liquid commercial heparin (Abbott)

(c) Ten serology tubes (1 cm inside diameter by 8 cm long)

(d) Conical centrifuge tube graduated to 15 milliliters

(e) 10 ml pipette graduated to tip

(f) 20 ml syringe glass tipped with thin coating of light mineral oil

(g) 18 gauge needles 1½ inches long These must be sharp and should be cleansed with Haemasol and checked with hydrogen peroxide for evidence of peroxidase before drying with alcohol and ether

All glassware must be chemically clean and dry before using

2 Procedure

(a) *Pipetting the protamine solution* To each of the 10 serology tubes the protamine sulfate solution is added from a micropipette in increments of 0 02 ml (0 02 mg) beginning with 0 02 ml (0 02 mg) in the first tube and ending with 0 20 ml (0 20 mg) in the tenth tube The entire 10 tube range runs serially from 0 02 ml to 0 20 ml (0 02 mg to 0 20 mg)

(b) *Pipette heparin into the conical tube* With a micropipette deliver 0 10 ml (1 0 mg) liquid commercial heparin to the bottom of the conical centrifuge tube

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(c) *Venipuncture* Cleanse skin with alcohol and dry Apply tourniquet and make clean needle puncture Gently aspirate (preferably by venous pressure) 12 to 14 ml of blood If a good venipuncture is not accomplished on the initial puncture another needle should be used as tissue juice or small amounts of blood may introduce serious error The syringe should be free of air bubbles

(d) *Mixing the blood and heparin* Remove needle from syringe and allow the blood to run gently down the side of the conical tube containing 1 0 mg (0 1 ml) of heparin bringing the blood to the 11 ml mark Stopper the tube with rubber stopper and slowly invert 15 times to obtain reasonable mixing The remainder of the test may be done in the laboratory and should be completed within one hour If not pipetted at once inversion mixing is repeated immediately before use

(e) *Pipetting the blood* The 10 ml pipette is carefully filled with the heparinized blood mixture avoiding aspiration of air bubbles One milliliter of blood is allowed to flow down the side of each of the 10 tubes containing the protamine solution Each tube is shaken briskly eight to 10 times to obtain reasonable mixing *of the heparinized blood with protamine solution The entire* series of tubes is then allowed to stand undisturbed for one hour at room temperature before the end point is read The end point is defined in terms of the protamine content of the tube containing the least amount of protamine in which a solid clot has formed at this time

(f) *The end point* In a series of 100 normal male subjects all tubes containing 0 14 mg or more of protamine clotted Those tubes containing 0 12 mg or less remained fluid Two unexplained exceptions have been observed These did not clot with 0 14 mg protamine at the end of one hour but did clot into the normal range at the end of two hours In a similar series of normal dogs the end point was found to be 0 12 mg of protamine Hereafter the human normal end point is the one described In women this end point may be increased during the menstrual period Normally the clot appears firm and retracts in all tubes containing 0 14 mg of protamine or more and is entirely fluid in all the

tubes containing 0 12 mg or less after one hour Clot retraction however is slightly impaired in the tubes of high protamine con centration The effect of other mild to moderate blood deficien cies on reading the end point is minimized by reading at one hour This is especially true of thrombocytopenia and prothrombin de ficiency

3 SOURCES OF ERROR

(a) Moist or unclean glassware or needles

(b) Inaccurate measurement of protamine and/or heparin solu tions

(c) Poor venipuncture technique In all coagulation studies it is imperative that the blood flow is prompt and free

(d) Failure to age protamine solution for 24 hours before use using protamine solution that has been standing for longer than one week or that has not been kept refrigerated The antiheparin activity can be checked by running a protamine titration on nor mal blood with each new batch of protamine solution

(e) Biologic variations that may occur in preparation of heparin It is advisable to check each new vial of heparin with the previous vial by running a protamine titration on normal blood using heparin from both vials before the supply from the one in use is exhausted

(f) Failure to obtain adequate mixing of either heparin with the original blood or of the heparinized blood with the protamine solutions In the latter case clotting may appear sporadically in the series of protamine tubes

(g) Gelation In some cases gelation precedes or substitutes for coagulation This problem is best resolved by reading as the end point the tube in which gelation first appears

(h) Undiagnosed hemophiliac or prothrombin deficient bloods These conditions may increase the protamine titration

(i) Clotting within normal range (0 14 mg of protamine) after 1 hour As previously stated normal blood and most abnormal blood specimens show no further clotting after one hour An oc casional blood sample however may show an increase in the pro tamine titration at the end of one hour but clot within the normal

(c) *Venipuncture.* Cleanse skin with alcohol and dry. Apply tourniquet and make clean needle puncture. Gently aspirate (preferably by venous pressure) 12 to 14 ml. of blood. If a good venipuncture is not accomplished on the initial puncture another needle should be used as tissue juice or small amounts of blood may introduce serious error. The syringe should be free of air bubbles.

(d) *Mixing the blood and heparin.* Remove needle from syringe and allow the blood to run gently down the side of the conical tube containing 1.0 mg. (0.1 ml.) of heparin bringing the blood to the 11 ml. mark. Stopper the tube with rubber stopper and slowly invert 15 times to obtain reasonable mixing. The remainder of the test may be done in the laboratory and should be completed within one hour. If not pipetted at once, inversion mixing is repeated immediately before use.

(e) *Pipetting the blood.* The 10 ml. pipette is carefully filled with the heparinized blood mixture avoiding aspiration of air bubbles. One milliliter of blood is allowed to flow down the side of each of the 10 tubes containing the protamine solution. Each tube is shaken briskly eight to 10 times to obtain reasonable mixing of the heparinized blood with protamine solution. The entire series of tubes is then allowed to stand undisturbed for one hour at room temperature before the end point is read. The end point is defined in terms of the protamine content of the tube containing the least amount of protamine in which a solid clot has formed at this time.

(f) *The end point.* In a series of 100 normal male subjects all tubes containing 0.14 mg. or more of protamine clotted. Those tubes containing 0.12 mg. or less remained fluid. Two unexplained exceptions have been observed. These did not clot with 0.14 mg. protamine at the end of one hour but did clot into the normal range at the end of two hours. In a similar series of normal dogs the end point was found to be 0.12 mg. of protamine. Hereafter the human normal end point is the one described. In women this end point may be increased during the menstrual period. Normally the clot appears firm and retracts in all tubes containing 0.14 mg. of protamine or more and is entirely fluid in all the

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tube (0 14 mg of protamine) after several hours It has been our experience that these otherwise normal individuals show no significant clotting abnormality In a few instances a similar decrease in the protamine titration occurred in bleeding cases but these generally did not return to the normal range

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This Book

THROMBOEMBOLIC CONDITIONS
AND THEIR
TREATMENT WITH ANTICOAGULANTS

By

CHARLES D MARPLE M D

and

IRVING S WRIGHT M D

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